FORMULATION AND EVALUATION OF GLUCOSAMINE HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLETS

Dissertation

Submitted in partial fulfillment of the requirement for the award of the degree of

MASTER OF PHARMACY

IN

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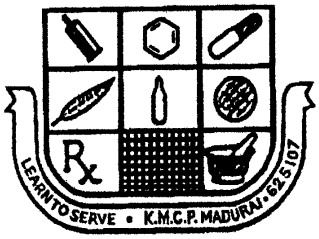

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CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF GLUCOSAMINE HYDROCHLORIDE SUSTAINED RELEASEMATRIX TABLET**" submitted by **CH.V.Lakshmi** to Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the award of Master of Pharmacy in Pharmaceutics at K.M. College of Pharmacy, Madurai, is a bonafide work carried out by her under my guidance and supervision during the academic year 2011-2012.

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ABBREVIATIONS

SR	Sustained Release
ICH	International Conference for Harmonization
USP	United States Pharmacopoeia
% RH	Percentage relative humidity
PVP	Poly (vinyl pyrrolidone)
HPMC	Hydroxy propyl cellulose
TI	Therapeutic index
UV	Ultra Violet
FTIR / IR	Fourier transform infrared / Infrared
λ max	Wavelength of maximum absorbance
S.D	Standard Deviation
CDR	Cumulative drug release
ADR	Amount of drug remaining
w/w	Weight/weight
ml	Milliliter's
cm	Centimeter's
nm	Nanometer's
Rpm	Revolutions per Minute
%	Percentage
^{o}C	Degree Celsius
mg	Milligram
GIT	Gastrointestinal tract
HPMC	Hydroxypropylmethyl cellulose
AUC	Area undercurve
IPA	Isopropylalcohol
BP	British Pharmacopoeia

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Dedicated to My Beloved Parents and Friends

1. INTRODUCTION

Societal pressures to reduce healthcare costs, coupled with the pharmaceutical industries need to maintain its economic incentive to develop new drugs, have required that the industry increase speed to market and reduce the number of failures and overall cost of new drug development. This need has made it imperative for the industry to use efficient, systematic approaches to both drug discovery and formulation design.

Oral drug delivery known for decades is the most widely utilized routes for administration among all routes that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms. Popularity of the route may be ease of administration as well as traditional belief that by oral administration the drug is well absorbed like food stuff ingested daily. Sustained release (SR) or Controlled release (CR) pharmaceutical products have over the past decade gradually gained medical acceptance and popularity since, their introduction into the market has received regulatory approval for marketing and their pharmaceutical superiority and clinical benefits over immediate release pharmaceutical products have been increasingly recognized. Sustained release oral dosage forms have brought new lease of life into drugs that have lost market potential due to requirement of frequent dosing, dose related toxic effects and gastro intestinal disturbance.

1.1 SUSTAINED RELEASE DELIVERY SYSTEM.[1, 2]

The term 'Sustained Release' is known to have existed in the medical and pharmaceutical literature for many decades. Sustained release has been constantly used to retard the release of therapeutic agent such that its appearance in the circulation is steadily maintained and its plasma profile is prolonged. The onset of its pharmacological action is often delayed and duration of therapeutic action is sustained.

In the recent years sustained release (SR) dosage forms continue to draw attention in the research for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release, sustained action, prolonged action and extended action are the terms used to identify drug delivery system that are designed to achieve a prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Sustained release

technology is relatively new field and as a consequence, research in this field has been extremely fertile and has produced many discoveries. New and more sophisticated controlled release/sustained release delivery system are constantly being developed and tested.

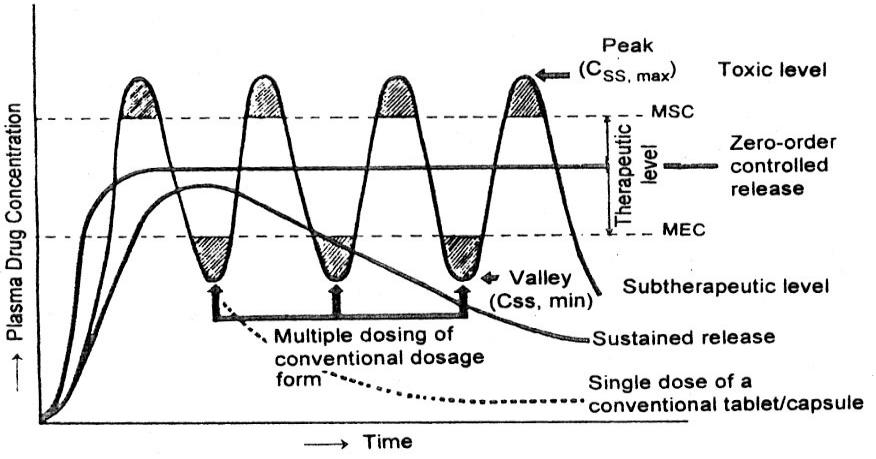
I] OBJECTIVES OF SUSTAINED RELEASE DRUG DELIVERY SYSTEMS.[3]

In general the goal of sustained release dosage form is to maintain therapeutic blood or tissue level of the drug for extended period of time. This is generally accomplished by attempting to obtain "zero order" release from the dosage form. Zero order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system. Sustained release systems generally do not attain this type of release and usually try to mimic zero order release by providing drug in slow "first order" fashion (i.e. concentration dependent). Thus sustained release dosage form is dependent. The sustained release dosage form consists of two parts:-

[1] An immediately available dose to establish the blood level quickly in an amount sufficient to produce the desired Pharmacological response i.e. (Loading dose).

[2] The remaining amount of total dose (maintenance dose) is then gradually released to maintain constant blood level of the drug.

FIGURE: 1



A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations

B] CLASSIFICATION OF SUSTAINED RELEASE FORMULATIONS.[4, 5]

The sustained release dosage forms are categorized on the basis of structural and physical appearance such as single unit dosage form, multiple unit dosage form and mucoadhesive delivery systems.

II) SINGLE UNIT DOSAGE FORMS:-

This refers to diffusion controlled systems where the drug is uniformly distributed (dissolved/dispersed) throughout the solid matrix or encapsulated by the polymer blend. This system can be classified as follows.

A] Complex reservoir system or multilayered system or coated tablets:-

The core material which usually, the drug alone or blended with hydrophilic or hydrophobic inert material, is compressed into tablets, which is then coated with a hydrophobic or semi permeable film of polymer or a mixture of both. The release is controlled by the number of barriers.

B] Osmotic Devices:-

The device is fabricated from a tablet that contains water soluble osmotically active drug, or that is blended with osmotically active diluents, by coating the tablet with semi permeable membrane barrier. Since barrier is permeable only to water, initial penetration of water dissolves the outer part of the core resulting in the development of osmotic pressure difference across the membrane. The device then delivers a volume of saturated solution equal to the volume of water uptake through membrane.

C] Monolithic Devices:-

If the release rate is controlled or sustained by incorporating hydrophobic fillers within the matrix then the system is called monolithic device, where diffusion of drug through the matrix is rate limiting step.

a) Floating tablets or capsules:-

These are designed to retain the drug in the stomach for extended period of time, by making the tablet to float in gastric juice at the stomach. This approach is suitable to the drugs which are liable to either degradation or poorly absorbed in distal part of GI tract.

b) Hydrophobic/swellable tablets:-

Opium alkaloid such as morphine salts homogenized with a fatty acid or its salt and any ethylene vinyl acetate copolymer (hydrophobic filler) and then compressed into tablets was reported to give sustained release pattern of the drug during *invitro* studies.

c)Semisolid matrix:-

Here drug is incorporated in an oily "semisolid" hydrophobic carrier (hydrogenated castor oil), and finally mass is usually filled into a gelatin capsule to repair dosage form.

III) MULTIPLE UNIT DOSAGE FORMS:-

It represents a combination of the dosage form, the source of which may either be homogeneous or heterogeneous. It offers the advantage of combining two or more drugs, in a single dosage form where the patient requires combination therapy. Another advantage is to release one of the parts of the same can be sustained release. These are also useful where drug excipient and drug interactions are inevitable in a single unit dosage form. The various forms which are available are:

A] Microgranules/spheroids:-

Drugs wet granulated alone or incorporated into inert granules, and then coated to control the release pattern.

B] Beads:-

Beads are prepared from various polymers and other inert materials that have been used as carrier to deliver the water soluble drugs orally in the form of sustained release preparation.

C] Pellets:-

Pellets are prepared by coating inert drug pellets with film forming polymers. The drug release depends upon coating composition of polymers and amount of coating.

D] Microcapsules:-

Microcapsules are prepared by applying relatively thin coating to small particles of solids, droplet of liquid and dispersions. Its uniqueness lies in smallness of particles and their use and adaptation to a wide variety of dosage forms.

IV) MUCOADHESIVE DELIVERY SYSTEM.

It utilizes principle of bio-adhesion for optimum delivery of the drug from the device. Bio-adhesion is defined as the occurrence in which one biological substance is adhered to another substance which may either be biological or non biological origin. If the substrate is mucosal membrane, the phenomenon is known as "muco-adhesion". Mucoadhesive system is suitable to increase the contact time of drug with absorbing membrane and localization of delivery of drug at targeted sites.

V) CHARACTERISTICS OF DRUGS UNSUITABLE FOR ORAL SUSTAINED RELEASE FORMS:-[6]

1. Short biologic half-lives (< 1h), Long biologic half-lives (>12 h).
2. Not effectively absorbed in the lower intestine.
3. Large doses required (>1g).
4. Cumulative action and undesirable side effects; drugs with low therapeutic indices.
5. Precise dosage is required to individual in case of anticoagulants, cardiac glycosides.

VI) DRAWBACKS OF CONVENTIONAL DOSAGE FORMS:-[7]

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

VII) POTENTIAL ADVANTAGES AND DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORMS:-[4, 6, 8]

a) ADVANTAGES:-

(i) Therapeutic advantage:-

Reduction in drug plasma level fluctuation; maintain a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

(ii) Reduction in adverse side effects:-

Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms.

(iii) Patient comfort and compliance:-

Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.

(iv) Reduction in healthcare cost:-

The total cost of therapy of the sustained release product could be comparable or lower than the immediate release product. With reduction in side effects, the overall expense in disease management also would be reduced.

(v) Avoid night time dosing:-

It is also good for patients to avoid the dosing at night time.

b)DISADVANTAGES:

(i) Dose dumping.

Dose dumping is a phenomenon where by relatively large quantities of drug in a sustained release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital.

(ii) Less flexibility in accurate dose adjustment.

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. But sustained release property may get lost, if dosage form is fractured.

(iii) Poor *In vitro – In vivo* correlation.

In sustained release dosage form, the rate of drug release is deliberately reduced to a large region of gastrointestinal tract. Hence it is called as 'Absorption window' which becomes important and may give rise to unsatisfactory drug absorption *invivo* despite excellent *invitro* release characteristics.

(iv) Patient variation.

The time period required for absorption of drug release from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

1.2 FACTORS INFLUENCING ORAL RELEASE DOSAGE FORMS.[9]

A] PHYSICO-CHEMICAL PROPERTIES.

i) MOLECULAR SIZE AND DIFFUSIVITY.

The ability of a drug to diffuse in polymers, its so-called diffusivity (diffusion coefficient *D*), is a function of its molecular size (or molecular weight). For most polymers, it is possible to relate log *D* empirically to some function of molecular size as

$$Log\ D = -s_v\ log\ u + k_v = -s_M\ log\ M + k_m$$

Where, *v* is molecular volume, *M* is molecular weight, s_v, s_M, k_V and k_m are constants. The value of *D* thus is related to the size and shape of the cavities as well as size and shape of drugs. The diffusion co-efficient of intermediate molecular weight drug i.e;100 to 400 Daltons, through flexible polymer ranges from 10^{-6} to 10^{-9} cm^2 /sec. For drugs having molecular weight > 500 Dalton the diffusion co-efficient in many polymer are very less i.e.; less than 10^{-12} cm^2 / sec. Drugs with large molecular size are poor candidates for oral SR drug delivery system because it is very difficult to control release rate of medicament from dosage form e.g. proteins and peptides.

ii) AQUEOUS SOLUBILITY.

As the drug must be in solution form before absorption, drugs having low aqueous solubility usually suffer oral bioavailability problem due to limited GI transit time of undissolved drug and limited solubility at absorption site. So these types of drugs are undesirable. Drugs having extreme aqueous solubility are undesirable for SR because, it is too difficult to control release of drug from the dosage form. Physiological pH dependent solubility i.e. variation in solubility at different GI pH values are undesirable (e.g. Aspirin, which is less soluble in stomach, but more soluble in intestine) as it will yield variation in dissolution rate. A drug with good aqueous solubility pH independent solubility is desirable for oral new drug delivery systems. The Bio-pharmaceutical Classification (BCS) System allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral drug absorption.

Classification of drugs according to Bio-pharmaceutical classification system.

Class I: High solubility-High permeability
Class II: Low solubility High permeability
Class III: High solubility Low permeability
Class IV: Low solubility-Low permeability

High solubility: Largest dose dissolves in 250 ml of water over a P^H range 1-8

High permeability: Extent of absorption is > 90%

Class III and Class IV drugs are poor candidates for SR/CR dosage forms.

Examples of drugs which are poor candidates for SR/CR release systems.

1. Drugs which are limited in the absorption by their dissolution rates are digoxin, warfarin, griseofulvin, and salicylamide.
2. Drugs poorly soluble in the intestine (acid soluble basic drugs): diazepam, diltiazem, cinnarizine, chlordiazepoxide, and chlorpheniramine.
3. Drugs having lower solubility in stomach: furosemide.

iii) IONIZATION CONSTANT(pK_a).

As we know only unionized drugs are absorbed and permeation of ionized drug is negligible, since its rate of absorption is 3 to 4 time less than that of the unionized drug. The PKa range for acidic drug where ionization is pH sensitive is around 3.0 - 7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0 – 11.0 are ideal for optimum positive absorption. Drugs shall be non-ionized at the site to an extent 0.1 – 5%. Drugs existing largely in ionized form are poor candidates for oral SR drug delivery system e.g. Hexamethonium.

iv) PARTITION COEFFICIENT.

As biological membranes are lipophilic in nature through which the drug has to pass through, the partition co-efficient of drug influences the bioavailability. Drugs having lower partition co-efficient values less than the optimum activity are undesirable for oral SR drug delivery system, as they have very less lipid solubility and the drugs will be localized at the first aqueous phase when they come in contact viz, Barbituric acid. Drugs having higher partition co-efficient values greater than the optimum activity are undesirable for oral SR drug delivery system because more lipid soluble drugs will not partition out of the lipid membrane once they get in to the membrane. The value of partition co-efficient at which optimum activity is observed is approximately 1000 : 1 in 1-octanol / water system.

A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes (i.e., its membrane permeability) in its apparent oil/water partition coefficient, defined as

$$K = C_O/C_W \qquad \text{-------- (1)}$$

Where C_O is the equilibrium concentration of all forms of the drug in an organic phase at equilibrium, and C_W is the equilibrium concentration of all forms in an aqueous phase. In general, drugs with extremely large values of K are very oil-soluble and will partition into membranes quite readily. The relationship between tissue permeation and partition coefficient for the drug generally is defined by the ***Hansch correlation***, which describes a parabolic relationship between the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient.

v) STABILITY.

One important factor for the loss of drug is through acid hydrolysis and/or metabolism in the GIT when administered orally. It is possible to improve significantly the relative bioavailability of a drug that is unstable in GIT by placing it in a slowly available controlled release form, for those drugs that are unstable in the stomach the most appropriate controlling unit would be one that releases its content only in the intestine. The release in the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its contents, only in the stomach. So, drugs with significant stability problems in any particular area of the GI tract are less suitable for formulation into controlled release systems that deliver the contents uniformly over the length of GI tract.

Acid unstable drugs (stomach).

Examples: Rabeprazole, pantoprazole, omeprazole, lansoprazole, esomeprazole, rifamipicin, mesalazine, erythromycin, riboflavin

Alkaline unstable drugs (drugs that are unstable in intestine and colon):

Ex: Captopril, ranitidine.

vi) DOSE SIZE.

If a product has dose size > 0.5g it is a poor candidate for oral SR drug delivery system, because an increase in bulk of the drug, leads to increase the volume of the product.

1.2.2 BIOLOGICAL FACTORS. [10]

i) ABSORPTION

The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into a sustained release system. Since the rate limiting step in drug delivery from a sustained release system is its release from a dosage form, rather than absorption. A rapid rate of absorption of drug relative to its release is essential if the 'system is to be successful'.

1. Drugs absorbed by active transport system are unsuitable for sustained/controlled drug delivery system: methotrexate, enalapril, riboflavin, pyridoxine, 5-fluorouracil, 5-bromo uracil, nicotinamide, fexofenadine, methyl-dopa.
2. Drugs absorbed through amino acid transporters in the intestine: cephalosporins, gabapentine, baclofen, methyl-dopa, levo-dopa.
3. Drugs transported through Oligo-peptide transporters, captopril, lisinopril, cephalexine, cefadroxil, cefixime.
4. Drugs required to exert a local therapeutic action in the stomach are unsuitable for sustained /controlled drug delivery.

   Ex: misoprostol, 5-fluorouracil, antacids, anti-helicobacter pylori agents.

b) ABSORPTION WINDOW.

Some drugs display region specific absorption which is related to differential drug solubility and stability in different regions of GIT, as a result of changes in environmental pH, degradation by enzymes, etc. These drugs show absorption window, which signifies the region of G.I tract where absorption primarily occurs. Drugs release from sustained/controlled release systems, after absorption window has been crossed with little/no negligible absorption. Hence absorption window can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of sustained/controlled release drugs.

Examples of Drugs exhibiting the site specific absorption in stomach or upper parts of small intestine (absorption window) are**:**

Acyclovir, captopril, metformin, gabapentin, atenolol, furosemide, ranitidine, levo-dopa, sotalol, salbutamol, riboflavin, sulfonamides, loratadine, cephalosporines, tetracyclines, verapamil, thiamine, sulpiride, baclofen, nimesulide, cyclosporine, quinolines.

c) DISTRIBUTION.

The distribution of a drug into vascular and extra vascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution is the ratio of drug concentration in the tissue to that in plasma at the

steady state called therapeutic ratio. The magnitude of the apparent volume of distribution can be used as a guide for addition studies and as a predictor for a drug dosing regimen and hence the need to employ a sustained release system.

d)METABOLISM.

Drugs with extensive metabolism are not suitable for SR drug delivery systems. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first-pass effect is poor candidate for SR drug delivery system, since it will be difficult to maintain constant blood level i.e. levodopa, nitroglycerine. Fluctuating drug blood levels due to intestinal metabolism upon oral dosing:

Examples: Salicylamide isoproterenol, clonazepam, hydralazine and levodopa.

Fluctuating drug blood levels due to first pass hepatic metabolism upon oral dosing:

Examples: Nortriptyline, phenacetin, morphine, propranolol.

Fluctuating blood levels due to enzyme induction are poor candidates for Sustained/controlled Release dosage forms:

Examples: Griseofulvin, phenytoin, primidone, barbiturates, rifampicin.

Fluctuating blood levels due to enzyme inhibition are poor candidates for Sustained/Controlled Release dosage forms:

Examples: Isoniazid, cimetidine, amiodarone, erythromycin, fluconazole, ketoconazole, mao –inhibitors, para - aminosalicyclic acid, allopurinol, coumarins.

e) HALF LIFE.

A drug having biological half-life between 2 to 8 hours is best suited for oral SR drug delivery system. If the biological half-life of a drug is < 2 h the system will require unacceptably large dose, whereas the biological half-life is > 8 h formulation of such drug into oral SR drug delivery system is unnecessary.

f) DRUG -PROTEIN BINDING.

The pharmacological response of drug depends on unbound drug concentration rather than total drug concentration and all drugs bound to some extent to plasma and or tissue proteins. Protein binding of drug plays a significant role in its

therapeutic effect regardless the type of dosage form as extensive binding to plasma increases the biological half-life and thus sometimes SR drug delivery system is not required for this type of drugs.

The role of protein binding as a factor in formulation of S.R/C.R dosage forms can be explained by considering angiotensin-II antagonist class of drugs. The drugs of this class are highly protein bound (>99%). Tasosartan is a long acting AT-II receptor blocker with a protein binding of 99.8%, while it's long acting active metabolite; Enoltasosartan has a protein binding 99.9%.

g) DISEASE STATE.

Even, in some cases are considered before the designing of an oral sustained delivery. This can be explained by the following classical examples. Aspirin is a drug of choice for rheumatic arthritis, and it is not a suitable candidate for sustained release dosage form. Still an aspirin sustained release dosage form could be advantageous to maintain therapeutic concentrations, particularly throughout the night, thus alleviating morning stiffness.

h) THERAPEUTIC INDEX.

It is most widely used to measure the margin of safety of a drug.

$$TI = TD_{50} / ED_{50}$$

The longer the value of Therapeutic index (TI), the safer the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products. A drug is considered to be safe if its Therapeutic value is greater than 10.

i) DOSES FORM INDEX.

It is the ratio of Css_{max} to Css_{min}. It is the goal of oral SR drug delivery system is to improve therapy by reducing the doses form index while monitoring the plasma drug level within the therapeutic window. So ideally the doses form index should be as close as to one.

1.3 SUSTAINED RELEASE MATRIX SYSTEMS.

A matrix tablet is the simplest and the most cost-effective method to fabricate an sustained-release dosage form. The majority of commercially available matrix formulations are in the form of tablets and their manufacture is similar to conventional tablet formulations consisting of granulation, blending, compression and coating steps. In its simplest form, a typical SR matrix formulation consists of a drug, release retardant polymer (hydrophilic or hydrophobic or both), one or more exipients (as filler or binder), flow aid (glidant) and a lubricant. Other functional ingredients such as buffering agents, stabilizers, solubilizers and surfactants may also be included to improve or optimize the release and/or stability performance of the formulation system.

These releases the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials.

1.3.1 CLASSIFICATION OF MATRIX TABLETS.[11, 12]

A] ON THE BASIS OF RETARDANT MATERIAL USED.

(i) Hydrophobic Matrices (Plastic matrices).

In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles.

Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers.

The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

(ii) Lipid Matrices.

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulations.

(iii) Hydrophilic Matrices.

A matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

Hydrophilic matrices are the most commonly used oral sustained-release systems because of their ability to provide desired release profiles for a wide range of drugs, robust formulation, cost-effective manufacture, and broad regulatory acceptance of the polymers. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups,

- Cellulose derivatives: methylcellulose 400 and 4000 cps, HPMC-25, 100, 4000 and 15000 cps and Sodium CMC.
- Noncellulose natural or semisynthetic polymers: agar-agar, Xanthan gum, carob gum, alginates, molasses, polysaccharides of mannose and galactose, chitosan and modified starches.
- Polymers of acrylic acid, corbopol 934, the most used variety.

(iv) Biodegradable Matrices.

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymatic process into olegomers and monomers that can be metabolized or excreted.

Examples are natural polymers such as proteins and polysaccharides; modified natural polymers synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

(v) Mineral Matrices.

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

B] ON THE BASIS OF POROSITY OF MATRIX.

Matrix system can also be classified according to their porosity and consequently, macroporous, microporous and non-porous systems can be identified.

(i) Macroporous Systems.

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1μm. This pore size is larger than diffusant molecule size

(ii) Microporous System.

Diffusion in this type of system occurs essentially through pores. For microporous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

(iii) Non-porous System.

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

C] ADVANTAGES OF MATRIX TABLETS.

- Easy to manufacture
- Versatile, effective and low cost
- It can be made to release high molecular weight compounds

D] DISADVANTAGES OF THE MATRIX SYSTEMS.

- The remaining matrix must be removed after the drug has been released.
- The drug release rates vary with the square root of time.
- Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

E] POLYMERS USED IN MATRIX TABLETS. [13]

The use of polymers in controlling the release of drugs has become important in the formulation of sustained release dosage form. Water soluble polymers may be used to increase the dissolution rates of poorly soluble drugs. Hydrogels provide the basis for implantation, transdermal and oral controlled release systems.

a) HYDROGELS.

- Polyhydroxyethylemethylacrylate (PHEMA)
- Cross-linked polyvinyl alcohol (PVA)
- Cross-linked polyvinyl pyrolidone (PVP)
- Polyethylene oxide (PEO)
- Polyacrylamide (PA)

b) SOLUBLE POLYMERS.

- Polyethylene glycol (PEG)
- Polyvinyl alcohol (PVA)
- Polyvinyl pyrrolidone (PVP)

c) SOLUBLE POLYMERS.

- Polyethylene glycol (PEG)
- Polyvinyl alcohol (PVA)
- Polyvinyl pyrrolidone (PVP)
- Hydroxypropyl methyl cellulose (HPMC)

d) BIODEGRADABLE POLYMERS.

- Polylactic acid (PLA)
- Polyglycolic acid (PGA)
- Polycaprolactone (PCL)

e) NONBIODEGRADABLE POLYMERS.

- Polyethylene vinyl acetate (PVA)
- Polydimethylsiloxane (PDS)
- Polyvinylchloride (PVC)
- Cellulose acetate (CA)
- Ethyl cellulose (EC)

f) MUCOADHESIVE POLYMERS.

- Polycarbophil
- Sodium carboxymethyl cellulose
- Polyacrylic acid
- Methyl cellulose
- Pectin

g) NATURAL GUMS.

- Xanthan gum
- Guar gum
- Karaya gum

1.4 MECHANISM OF HYDROPHILIC MATRIX TABLETS.[14, 15]

The mechanism of drug release from hydrophilic matrix tablets after ingestion is complex but it is based on diffusion of the drug through, and erosion of the outer hydrated polymer on the surface of the matrix. Typically, when the matrix tablet is exposed to an aqueous solution or gastrointestinal fluids, the surface of the tablet is wetted and the polymer hydrates to form a gelly-like structure around the matrix, which is referred to as the "gel layer". This process is also termed as the glassy to rubbery state transition of the (surface layer) polymer. This leads to relaxation and swelling of the matrix which also contributes to the mechanism of drug release.

The core of the tablet remains essentially dry at this stage. In the case of a highly soluble drug, this phenomenon may lead to an initial burst release due to the presence of the drug on the surface of the matrix tablet. The gel layer (rubbery state) grows with time as more water penetrates into the core of the matrix, thereby increasing the thickness of the gel layer and providing a diffusion barrier to drug release. Simultaneously, as the outer layer becomes fully hydrated, the polymer chains become completely relaxed and can no longer maintain the integrity of the gel layer, thereby leading to disentanglement and erosion of the surface of the matrix. Water continues to penetrate towards the core of the tablet, through the gel layer, until it has been completely eroded.

Soluble drugs can be released by a combination of diffusion and erosion mechanisms whereas erosion is the predominant mechanism for insoluble drugs. For

successful sustained release of drugs, it is essential that polymer hydration and surface gel layer formation are quick so as to prevent immediate tablet disintegration and premature drug release. For this reason, polymers for hydrophilic matrices are usually supplied in small particle size to ensure rapid hydration and consistent formation of the gel layer on the surface of the tablet. A large number of mathematical models have been developed to drug release profiles from matrices. The simple and more widely used model is the one derived by *Korsemeyer et al*. and is as follows:

$$Mt / M\alpha = k\ t\ n \text{---------- (1)}$$

Where,

Mt / Ma is the fraction of drug release

'k' is the diffusion rate constant

't' is the release time

'n' is the release exponent indicative of the mechanism of drug release.

The equation was modified by *Ford et al*. to account for any lag time or initial burst release of the drug

$$Mt / Ma = k\ (t - 1)\ n \text{ ---------- (2)}$$

Where, l = lag time.

It is clear from both equations that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics (also termed as case II transport). Here, the polymer relaxation and erosion are the rate-controlling steps. When n = 0.5, *Fickian diffusion* is the rate-controlling step (case I transport). Values of n between 0.5 and 1 indicate the contribution of both the diffusion process as well as polymer relaxation in controlling the release kinetics (non-*Fickian,* anomalous or first-order release). It should be noted that the two extreme values of n = 0.5 and 1 are only valid for slab geometry.For cylindrical tablets, these values range from $0.45 < n < 0.89$ for *Fickian*, anomalous or case II transport respectively.

In general, two major factors control the drug release from swelling controlled matrix system. They include

1. The rate of aqueous medium infiltration into the matrix, followed by a relaxation process (hydration, gelatin or swelling)

2. The rate of matrix erosion

As a result of these simultaneous processes, two front are evident, a swelling front, where the polymer get hydrated, and an eroding front. The distance between these two fronts are called diffusion layer thickness.

Diffusion layer thickness depends on the selective rate at which the swelling and eroding fronts move in relation to each other. If the polymer gets slowly, solvent can penetrate deep into the glassy matrix thus dissolving the drug; therefore gel layer thickness and it stability are council in controlling drug release.

Swelling of HPMC matrix tablet was higher for a high molecular weight. They attributed this to the large hydrodynamic volume occupied by high molecular weight chain when hydrated. As the polymer chain becomes more hydrated and the gel becomes more dilute, the disentanglement concentration may be reached that is, the critical polymer concentration was below in which the polymer chain disentangle and detached from gelled matrix.

Matrix Dissolution control:[16,17]

In this system an alternative approach is to compress the drug with a slow dissolving carrier. Here the rate of drug release is controlled by the rate of penetration of the dissolution fluid into the matrix, porosity, presence of hydrophobic additives and the wettability of system and surface of particle

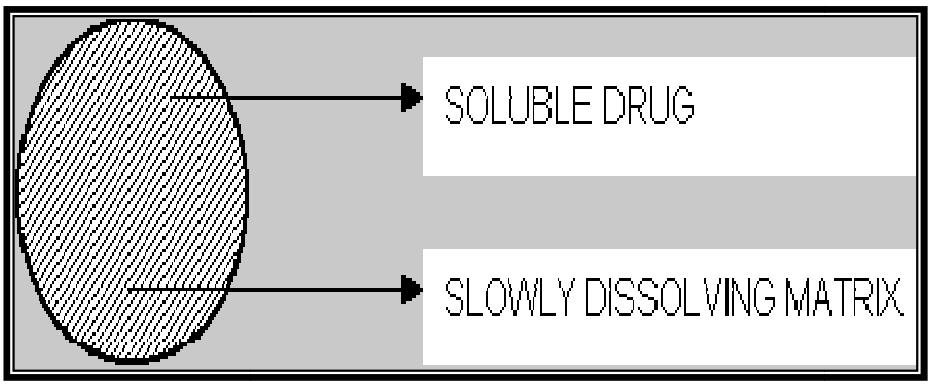


Fig: 2 Matrix dissolution controlled drug delivery

1.5 DRUGS SUITABLE FOR SUSTAINED RELEASE FORMULATIONS.[18,19]

Not all drugs lend themselves to the formulation of a sustained release product. The important factors that are to be considered in the choices of a drug as a candidate of SR preparations are as follows.

a) Biological half-life

Only drugs with short biological half lives (2-4 hours) make good candidates for SR systems, but a larger dose may be required to maintain high release rate.

Conversely, drugs with long half-lives can be given at less frequent intervals and hence there is no advantage in formulating these drugs as sustained release formulations.

The pharmaceutical effect of some drugs with short half-lives is sustained by various mechanisms.

- The drug binds to the tissues.

Eg: Tissue-bound angiotensin convering enzyme(ACE) inhibitors. For these drugs, less frequent dosing is needed even though the drug is having a shorter half-life.

- The drugs have irreversible effects

Eg. The inhibition of platelet cycloxygenase by aspirin.

- The relationship between response and plasma / blood concentration is relatively flat or if the dose given results in concentrations which are in the plasma region of the dose response relationship.

Eg: - Thiazides in hypertension.

- The drug is metabolized to pharmacologically active metabolite (s) which are more slowly cleared than the parent drug.

Eg:- Quinapril, Trandolapril, Venlafaxine

b) Therapeutic range

Drugs that are highly potent such as cardiac glycosides should not be considered for SR preparations due to loss in flexibility in dosage regimen and potential sudden dose dumping.

c) GI absorption

Most SR formulations are dissolution controlled; release rate from the dosage from being the rate-limiting step. Once the drug is released, it is transferred from the intestinal lumen to the blood. Therefore efficient drug absorption from GIT is a prerequisite for oral controlled release dosage forms.

d) Stability to wide pH range, GI enzymes and flora

For an orally administered drug, stability in the GI contents is necessary to ensure complete and reproducible drug input into the body, since drug will be exposed to luminal contents. Unlike conventional dosage forms, a SR formulation is exposed to the entire pH range and enzymes. In colonic absorption, stability to metabolizing effect of colonic bacteria is also required.

e) First pass metabolism

Hepatic metabolism may render a drug unsuitable for oral SR release. This is because systemic availability for such a drug is highly reduced when input rate is small.

1.5.1 STABILITY OF THE SUSTAINED ACTION DOSAGE FORM DURING STORAGE.[20]

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the format stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance.

a)SELECTION OF BATCHES.

Data from stability studies should be provided on at least three concurrent batches of the drug product. The primary batches should be of the same formulation and packaged in a same type of package as proposed for marketing. The manufacturing process used for primary batches should simulate that, to be applied to production batches and should provide product of the same quality & making the same specification as that intended for marketing. Two of the three batches should be at least pilot-scale batches & the third one can be smaller.

b) SPECIFICATION.

Specification, which is the list of tests, reference to analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications.

Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and likely to influence quality, safety and efficiency. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content and functionality tests (e.g. for a dose delivery system). Analytical procedures should be fully validated and stability indicated.

c) TESTING FREQUENCY.

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For a product with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should minimum of 3 months over the first year, every 6 months over the second year and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3, and 6 months), from a 6 month study is recommended. When testing at the immediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final points (e.g. 0, 6, 9, and 12) from a 12 month day is recommended.

d) STORAGE CONDITIONS.

In general, a drug product should be evaluated under storage conditions that test its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long-term testing should cover a minimum of 12 months duration or at least three batches at the time of submission and should, be continued for a period of the sufficient time by covering the proposed shelf life. Long-term, accelerated and where appropriate, intermediate storage conditions for drug products are detailed in sections below.

Table 1. Storage Conditions for Stability Studies.

Study	Storage condition	Minimum Time Period Covered by data at submission
Long term	$25^0C \pm 2^0C/60\%$ RH ± 5% RH	12 months
Intermediate	$30^0C \pm 2^0C/60\%$ RH ± 5% RH	6 months
Accelerated	$40^0C \pm 2^0C/75\%$ RH ± 5% RH	6 months

When "significant change" occurs at any time during 6 months testing at the accelerated storage condition, additional testing at the immediate storage condition should be conducted and evaluated against significant change criteria.

In general significant change for a drug product is defined as:

1) A 5% change in assay from its initial value; or failure to meet the acceptance criteria for when using biological or immunological procedures.
2) Any degradation products exceeding its acceptance criterion.
3) Failure to meet the acceptance criterion for appearance, physical attributes, and functionality test. Eg: - Hardness, dose delivery per activation however, some changes in physical attributes may be expected under accelerated conditions and as appropriate for the dosage form.
4) Failure to meet the acceptance criterion for pH.
5) Failure to meet the acceptance criterion for dissolution for 12 dosage units.

Storage conditions are maintained as stated in ICH guidelines. The globalization and increase in worldwide trade in recent has led to the need for international drug approvals and unification of regularly requirements & evaluation products. ICH has already a number of harmonized guidelines providing guidance on generation of data that would be acceptable in the European Union, Japan & USA.

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf life. The stability protocol used for studies on commitment batches should be the same as that for the primary batches.[18]

e) EVALUATION.

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form. The purpose of the stability study is based on the testing a minimum of three batches of drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances.

2.1 LITERATURE REVIEW ON GLUCOSAMINE:-

Gabriel herrero-beamont et al (2007)., studied the effects of glucosamine sulfate (1500mg administered once daily) for osteoarthritis during a 6month course by oral route of administration. The findings of study was that glucosamine sulfate at the oral once-daily dosage of 1500mg is more effective than placebo in treating osteoarthritis. Although acetaminophen also had a higher responder rate compared with placebo.[21]

S.Persiani et al (2007)., investigated the synovial and plasma glucosamine concentration in osteoarthritis patients following oral administration of crystalline glucosamine sulphate at a therapeutic dose of 1500mg once-daily-dose for 14days. The glucosamine was bioavailable both systemically and at the site of action after oral administration of crystalline sulphate in osteoarthritis patients. Steady state of glucosamine concentration in plasma and synovial fluid were correlated and in line with those effective in selected *invitro* studies.[22]

Ali Aghazazeh-habashi et al (2002)., studied the single dose pharmacokinetics of glucosamine by various routes of administration of hydrochloride salts to rats and to locate the site of its first pass metabolism. Serial blood samples were collected and determined by using HPLC. They found out that orally administered glucosamine is rapidly absorbed, highly distributed, and effectively cleaned.[23]

E. Roda et al (2005)., studied the pharmacokinetic data on glucosamine, limiting the understanding of glucosamine sulfate mechanism of action in support of its treatment effects in osteoarthritis. Glucosamine is bioavailable after oral administration of crystalline glucosamine sulfate, persists in circulation and its pharmacokinetics support once-daily dosage. Steady state peak concentration at the therapeutic dose of 1500 mg was in line, with those found to be effective in selected *invitro* mechanistic studies. Glucosamine elimination half-life was only tentatively estimated to average 15 h.[24]

M.Basak et al (2006)., studied the absorption of 2 different formulations of glucosamine sulfate in randomized, multi-dose, two ways, and crossover study. The novel timed release pellet filled Hard gelatin shell capsule (TimeOsamine^{TM}) was compared with a power-filled hard gelatin shell. The timed release capsule was used in double dose of 1000 mg (2 x 500 mg) with an interval of 12 h whereas filled hard gelatin capsule was used in triple dose of 1500 mg (3 x 500 mg) with an interval of 8 h after 10 h pre-dose fasting. The concentration of glucosamine was measured after 24h. Pharmacokinetics properties including area under curve AUC, Cmax, Tmax were measured. After reduction in the dose by 33 % the AUC_{0-24} of TimeOsamine^{TM} is 96.37% with respect to power-filled formulation AUC_{0-24} was compared.[25]

May M.Chou et al (2008)., examined the effects of chondroitin sulfate (CS) alone and CS plus glucosamine sulftate (GS) in a dietary bar formulation on inflammatory parameters of adjuvant-induced arthritis and on synthesis of interleukin-1β(1L-1β) and matrix metalloprotease-9 (MMP-9).The combination of chondroitin sulfate and glucosamine sulfate in a dietary bar more so than chondroitin sulfate ameliorates parameters of rheumatoid arthritis.[26]

S.Sandhya et al (2007)., studied the effect of glucosamine and glycosamineglycans on matrix metalloproteinase (MMPs) in type II collagen induced experimental arthritis. As MMPs appear to play a key role in the degradation of cartilage matrix in the progression of arthritic disease, MMPs are considered as potential therapeutic targets. The oligosaccharides treated animals showed considerably lower MMP activity (particularly MMP9) compared with arthritic control. The chondroitin sulfate A (and the oligosaccharides derived from it) not only reduced the activity of MMPs, indicating that the production of MMPs is affected. The antiarthritic effect of chindroitin sulphate A involves down-regulation of MMPs, which are critically involved in progression of arthritic disease.[27]

Sheila laverty et al (2005)., studied the concentration of glucosamine hydrochloride in the synovial fluid and its pharmacokinetics in serum in a large animal model following dosing with glucosamine hydrochloride at clinically relevant doses. It

provides both high reproducibility and high recovery of standard glucosamine hydrochloride as its acetylated derivative over the concentration range of interest for analysis of biologic fluids**.** The apparent therapeutic benefit of dietary glucosamine on pain and joint space width in humans and animals maybe secondary to its effects on nonarticular tissues, such as the intestinal lining, liver, or kidney, since these maybe exposed to much high levels of glucosamine following ingestion.[28]

Chanda kulkarniet et al (2011)., compared the safety and efficacy of Glucosamine hydrochloride- sustained release (GLU-SR) with that of Glucosamine hydrochloride immediate release (GLU-IR) in patients with knee osteoarthritis (OA). It involved 59 patients with knee OA, randomized to receive single oral dose of 1,500 mg, GLU-SR and GLU-IR for 60 days with 31 and 28 patients, respectively. The equal efficacy of the glucosamine formulations on algofunctional indices in reducing pain in patients with knee OA with less number of adverse events (AEs) in GLU-SR.[29]

S.Mahendran et al (2011) .,formulated and evaluated the sustained release matrix tablets of glucosamine sulfate influence of combination of hydrophilic and hydrophobic matrix formers which can release the drug up to time of 24 h in predetermined rate. The combination of hydrophilic and hydrophobic combination showed less result than use of alone. The *invitro* release data was well fit to Peppa's and Hixson Crowell release kinetics.[30]

Rikka mika et al (2005) .,formulated the controlled release tablets of N-acetyl-D-glucosamine (NAG), maltose monohydrate and maltopentaose by using hydrophobic matrix formers starch acetate (SA) and ethyl cellulose (EC). The optimized matrices, which had either low porosity and high drug load or high porosity and low drug load, released the saccharides within the desired 2–4 h. In the case of sustained release formulations, it was found that the release of maltose monohydrate and maltopentaose was biphasic and slower than the release rate of NAG from similar tablets. Both SA and EC matrices were found to represent suitable controlled oral delivery vehicles for saccharides.[31]

2.2 LITERATURE REVIEW ON SUSTAINED RELEASE TABLETS:-

Sourabh jain et al (**2008**)., formulated the sustained release tablets of furosemide by using pectin, guar gum and xanthan gum. *Invitro* release of drug was performed in phosphate buffer PH 7.2 for 15hrs. The tablet with guar gum was found to be greater swelling than those with pectin and xanthan gum. It is cleared through the dissolution profile of furosemide from matrix tablet which was prepared using different natural polymers were retarded approximately 15h.[32]

V.N.Deshmukh et al (2009)., developed the sustained release metoprolol succinate tablet using natural hydrophillic gums such as karaya gum and xanthan gum as a release modifier and showed the mechanism of drug release of metoprolol succinate by the diffusion mechanism.[33]

Hamdy abdelkader et al (2009)., formulated the controlled release baclofen matrix tablet by using different types and levels of hydrophilic matrixing agents including methylcellulose (MC) sodium alginate (ALG) and sodium carboxymethylcellulose (CMC) in an attempt to formulate controlled release matrix tablet containing 25mg baclofen and that compared with standard commercial tablets and showed the excipients used in this study did not alter physico-chemical properties of the drug and the prepared matrix tablet showed good mechanical properties.[34]

Gangaraobattu et al (2011)., formulated the sustained release matrix tablet of lornoxicam for maintaining therapeutic blood or tissue levels of drug for extended period of time by using an natural polymer “Tamarind seed polysaccharide (TSP). The tablets were formulated by wet granulation method using 10%, 20%, 30%, and 40% of TSP as a binding agent. After 24h the release profile of tablets with 20% TSP binder shows maximum drug release with tablets containing 40% TSP by increasing the percent of natural polymer (TSP) release rate decreased. The formulation with 20% of TSP follows zero order kinetics via swelling, diffusion and erosion.[35]

Afsar C.Shaikh et al (2011)., developed once-daily sustained release tablets of Aceclofenac sodium (200mg) by wet granulation using hydrophilic polymer like HPMC K100.The drug release of optimized formulations was shown to extend for 24h. The result showed that the release of drug can be extended by using suitable hydrophilic polymers in preparation of matrix based sustained release formulation of Aceclofenac.[36]

S.H. Lakade et al (2008)., formulated the Nicorandil matrix sustained release tablet which can release the drug up to time of 24 h in predetermined rate. The formulation of Nicorandil matrix tablet was prepared by the polymer combination of hydrophilic and hydrophobic in order to get required theoretical release profile. The *invitro* release rate profile should the higher concentration of F2 polymer in tablet, the combination of hydrophilic and hydrophobic combination showed less result than use of alone. The *invitro* release data was well fit to Peppa's and Hixon crowel release kinetics.[37]

M.R.Bhalekar et al (2008)., formulated the sustained release matrix tablet of diclofenac sodium by using black gram as sustained release matrix forming material in formulation by wet granulation technique using isopropyl alcohol as a granulating agent. Sustained release matrix tablets of diclofenac sodium, were developed by using different drug: polymer ratios, such as BF1 (1:1), BF2 (1:2), BF3 (1:3) and BF4 (1:4). Tablets prepared with Hydroxypropylmethylcellulose (HPMC 50cps) and Xanthan gum as matrix forming material for the comparative study. The dissolution profiles of the HF2 (HPMC 50cps) and XF1 (xanthan gum) matrix tablets were close to the profile obtained by seed flour of black gram based matrix tablets BF1 (black gram).The kinetic treatment showed that the release of drug follows zero order model and anomalous diffusion for BF1 and XF1 while the drug release of HF2 was best explained by Higuchi's model and anomalous diffusion.The seed flour of black gram possess substantial matrix forming property that could be used for sustained drug delivery.[38]

Uttam mandal et al (2007)., formulated and optimized the sustained release matrix tablet of metformin HCL 500mg using response surface methodology by non-aqueous wet granulation method using HPMC K15M and PVP K30 were used as matrix

forming polymer. The formulated tablets followed the higuchi drug release kinetics and diffusion was the dominant mechanism of drug release regulated the complete release within 8. Validation of optimization was performed, the percentage error of the mean was found to be (±S.D) 0.0437±0.385. By unraveling the study the effect of 2 factors on the *invitro* drug release helped in finding optimum formulation in sustained drug release.[39]

Shahanakhattak et al (2010)., formulated and evaluated controlled release matrix tablets of Losartan potassium using natural and synthetic polymers by direct compression method using different ratios of drug:polymer concentration. Fourier Transform Infrared Spectroscopy (FT-IR) and Differential Scanning Calorimetry (DSC) study revealed no chemical interaction between drug and polymers in a ratio of (1:1). Precompression and postcompression parameters complied with pharmacopoeial limit for the tablets. *In-vitro* release studies was performed and the results indicates that matrix tablet containing 50% w/w blend of natural and synthetic polymer has better controlled release for a period of 24 h.[40]

M.Harris shoaib et al (2006)., developed a once-daily sustained release matrix tablet of Ibuprofen using hydroxypropyl methylcellulose (HPMC) as release controlling factor and to evaluate drug release parameters as per various release kinetic models. Sustained release profile tablets were directly compressed using Avicel pH 101 and Magnesium stearate. The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model was based on linearity (coefficient of correlation). The drug release data fit well to the Higuchi expression. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion.[41]

Bhupendra.G.Prajapatti et al (2010)., formulated and evaluated the novel nicorandil sustained release matrix tablet based on the combination of hydrophilic and hydrophobic matrix system. Formulated tablets were also characterized by parameters like thickness, weight variation test, drug content uniformity, hardness, friability and the *invitro* release rate profile was compared with the marketed product's release profile with

the help of similarity factor (f2) value. Formulation prepared with HPMC K200M: Eudragit RSPO (1:1) indicates 94.46% of drug release at 22h and it has similarity factor (f2) value 68.07. Hydrophilic and Hydrophobic polymer combination showed 22h release using combination of hydrophilic or hydrophobic polymers.[42]

Margret Chandrin et al (2009)., formulated and evaluated the sustained release matrix tablets of Zidovudine by using different drug:polymer ratio. Kollidon SR, Hydroxy propyl methyl cellulose K15M, K100M as matrix former. All lubricated formulations were compressed by direct compression and by wet granulation method. Among the different formulation, B8 showed sustained release of drug for 12h with 86.55% release. The regression coefficient value of Higuchi plot was found to be 0.9925 that showed that drug was released by diffusion mechanism.Thus, drug in combination with Hydroxypropyl methylcellulose K100M were found to be effective in retarding the release of Zidovudine.[43]

Rakesh.K. Deore et al (2010)., formulated the oral sustained release matrix tablets of a mixture of both tramadol hydrochloride and glyceryl palmitostearate (GP) by melt granulation by direct compression (DC, 1:2 ratio). The MG4 showed the most suitable sustained release, 58.4 ± 1.1 % in 12 h ($p < 0.05$). Drug release (98.2 ± 0.2 % in 8 h) was highest for direct compression which was prepared by direct compression. The Glyceryl palmitostearate is a suitable matrix-forming agent to sustain the release of a water-soluble drug such as tramadol hydrochloride.[44]

Inez Jimenez-Martinez et al (2008)., developed and formulated the in vitro sustained release of captopril from Metolose SH 4000 SR/sodium bicarbonate floating tablets. It has been studied, various proportions of Metolose and bicarbonate at two different compaction pressures. The results shows that matrices compacted at 55MPa float in the dissolution medium for more than 8 h while those compacted at 165MPa float only when sodium bicarbonate is included in the formulation. The increase of the matrix polymer proportion increases the maximal hydration volume as well as the time to attain this maximum. The matrices hydration volume increases with the inclusion of sodium bicarbonate in the formulation.[45]

Eddy castellanos gil et al (2006)., developed and optimized the novel oral controlled delivery system of propranolol hydrochloride (PPL).. The sustained-release matrix tablets with good physical, mechanical and technological properties were obtained with a matrix excipient:PPL ratio of 60:40 (w/w), with a dextran:HPMC ratio of 4:1 (w/w) and with a cetyl alcohol amount of 15% (w/w). The value for the similarity factor ($f2 = 69.6$) suggested that the dissolution profile of the present two sustained-release oral dosage forms are similar. Higuchi (diffusion) and Hixon–Crowell (erosion) kinetic profiles were achieved and this codependent mechanism of drug releasewas established.[46]

A.Streubel et al (2002)., prepared and characterized single unit, floating controlled drug delivery systems consisting of (i) polypropylene foam powder, (ii) matrix-forming polymer(s), (iii) drug, and (iv) filler (optional). The highly porous foam powder provided low density and thus, excellent in vitro floating behavior of the tablets. All foam powder-containing tablets remained floating for at least 8 h in 0.1 N HCl at 37 8C. The release rate was effectively modified by varying the ‘‘matrix-forming polymer/foam powder’’ ratio.The floating behavior of the low density drug delivery systems could successfully be combined with accurate control of the drug release patterns.[47]

Thomas quinten et al (2009)., developed the injection moulded matrix tablets by using a mixtures of ethyl cellulose and low substitutednhydroxy propyl methyl cellulose. Formulations containing metoprolol tartrate (30%, model drug), ethylcellulose with dibutylsebacate (matrix former and plasticizer) and L-HPC were extruded and subsequently injection moulded into tablets (375 mg, 10mm diameter, convex-shaped) at different temperatures (110, 120 and 130 ◦C). Tablets containing 30% metoprolol and 70% ethylcellulose (EC 4cps) showed an incomplete drug release within 24 h (<50). The statistical design confirmed a significant influence of the EC and L-HPC concentration on drug release, while the processing temperature and EC viscosity grade did not affect drug release. [48]

S.I.Pather et al (1997)., formulated the sustained release theophylline matrix tablet by direct compression method by using ethylcellulose. In addition, matrices of this polymer display slow surface erosion which can be enhanced by the incorporation of a swelling agent. The release rate decreases because the external layers of the tablet become depleted and water must penetrate the deeper layers of the tablet to reach the remaining drug.. It was possible to sustain the release of a therapeutic dose of theophylline over a 12-h period. The erosion mechanism can be used to solve the problems associated with hydrophobic and plastic matrix tablets, i.e. the continuous reduction in the terminal release rate with time.[49]

Ghada ahmed abdel bary et al (2008)., developed an extended release matrix tablet of nicorandil; a freely water soluble drug used in cardiovascular diseases. Chitosan (CH)/hyaluronate sodium (HA), pectin (PE) or alginate sodium (AL) interpolymer complexes (IPCs) were prepared. The optimum IPCs (CH:HA, 40:60), (CH:PE, 30:70) and (CH:AL, 20:80) were characterized by Fourier transform infrared spectroscopy.. Nicorandil matrix tablets were prepared using the optimum IPCs, alone or in combination with Imwitor_ 900 K. Results of the dissolution studies revealed that formula F11 (CH:AL, 20:80) IPC:Imwitor_ 900 K, 3:1) could extend drug release >8 h.[50]

N.Tanaka et al (2005)., formulated a novel sustained-release (SR) system for poorly water-soluble drug nilvadipine by applying solid dispersion (SD) technique for improving the solubility. The developed SR system, disintegration-controlled matrix tablet (DCMT), consists of hydrogenated soybean oil (HSO) as wax and SD granules containing low-substituted hydroxypropylcellulose (L-HPC) as a disintegrant. The release rate of NiD from DCMT was controlled by the disintegration rate of tablet. The release profile of NiD was described by the Hixson–Crowell's model better than zero-order kinetics, first-order kinetics and Higuchi's model.[51]

S.Chopra et al (2007)., designed and optimized the sustained release dosage form of an anti-hypertensive agent, losartan potassium, using response surface methodology by employing a 3-factor, 3-level Box-Behnkenstatistical design. Independent variables studied were the amount of the release retardant polymers – HPMC K15M (X1), HPMC

K100M (X2) and sodium carboxymethyl cellulose (X3). In vitro release and swelling studies were carried out for the optimized formulation and the data were fitted to kinetic equations.The adjusted (0.9842) and predicted values (0.9893) of r2 for Y2 were in close agreement.. Tablets showed an initial burst release preceding a more gradual sustained release phase following a non-fickian diffusion process. [52]

S.Orenetal et al (1996)., studied the anti-hypertensive efficacy of combination of verapamil SR/ trandolapril 180/l mg o.d. for a period of 8 weeks. The average systolic and diastolic blood pressure was reduced by a statistically significant amount (11/9 mmHg) during the day) and 11/7 mmHg during the night (10.00 pm-8.00 am).. Two patients discontinued the study prematurely due to impotence which began during the placebo run-in period. No adverse events were serious or required any additional medical treatment. The fixed combination of verapamil SR and trandolapril appear to be a very effective and well-tolerated once-a-day antihypertensive medication.[53]

T.Kristmundsdottir et al (1996)., designed the release of diltiazem from eudragit microparticles by spraydrying technique using acrylate methacrylate copolymers. eudragit RS and RL as coating materials. The release pattern of diltiazem hydro chloride was affected by microparticles structure either as matrix or reservoir. The result shows that microparticles from eudragit acrylic resins RL and RS with a narrow particle size distribution. It is concluded that drug release rate can be controlled by polymer and spray drying technique.[54]

Harsh T Mulani et al (2011)., developed the characteristics of a new Polyvinylacetate/Povidone based excipient, Kollidon® SR were evaluated for application in extended release matrix tablets. The similarities in release profiles were evaluated by applying the model independent f2 similarity factor. A minimum concentration of 30% polymer was necessary to achieve a coherent matrix, able to extend the release of the incorporated drugs. Increasing the Kollidon® SR concentration in the tablet led to a slower drug release. Drug release follows square root of time dependent kinetics, thus indicating a diffusion-controlled release mechanism. It was concluded that Kollidon® SR is a potentially useful excipient for the production of pH-independent extended release matrix tablets.[55]

Prajapati B.G et al (2010)., developed hydrophilic polymer and hydrophobic polymer based matrix Losartan potassium sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. Formulation of Losartan potassium matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. In vitro release profile was checked for 24 hrs to evaluate the SR matrix tablet of Losartan potassium. From in vitro dissolution profile, Batch B4 was prepared with blend of HPMC K4M (67.2 mg), HPMC K200M (90mg) and Eudragit RSPO(112.5 mg), where drug release was about 94-98%. Batch B4 showed highest similarity factor values (f2 = 67.76).[56]

Nilesh.V.Ingle et al (2011)., developed the matrix tablets of Ambroxol Hydrochloride for Sustained Release.Hydroxy Propyl Methyl Cellulose (HPMC) K4M and Guar Gum as the retardant polymers and studied the effect of various formulation factors such as polymer proportion, polymer type and effect of filler type on the *invitro* release of the drug. *In vitro* release studies revealed that the release rate decreased with increase polymer proportion and hydrophobic polymers retard the drug release more than hydrophilic polymers. The formulations F7 sustained release of drug for 12 hrs with 91.56%. Because of swelling property increased the drug release profile to a small extent due to change in swelling at the tablet surface. [57]

M.Soumya et al (2011)., developed and optimized the bilayered sustained release matrix tablets of Valsartan. The tablets contained an immediate releasing layer with the loading dose of the drug and a sustaining layer with maintenance dose of drug prepared by wet granulation method. Sodium starch glycholate was used as super disintegrant and Eudragit RSPO and Eudragit RLPO were used as polymers. Formulation F9 was selected as an optimized one where the drug from immediate layer was released with in15 min and then sustained for a period of 12 hrs**.** Kinetic treatment to the *invitro* release data revealed that the drug release followed zero order non – fickian diffusion with n value greater than 0.45.[58]

S.Rajhans et al (2011)., designed a Swellable, gastro-retentive drug delivery system using combination of Polyethylene oxide (Polyox WSR 303) and HPMC K 100LV by wet granulation process. Aging (by accelerated Stability study) showed no significant difference in dissolution when a sample packed in HDPE bottle was stored at 40 ± 2°C / 75 ± 2 % RH conditions for 3 months. Based on the Release kinetics it can be concluded that this combination of Polyox WSR 303 and HPMC K 100 LV is particularly suitable as gastro retentive drug delivery system of Valsartan as extended release drug delivery system.[59]

Rajesh gollapudi et al (20011)., prepared a twice daily sustained release matrix tablets of losartannpotassium using Eudragit RLPO, RSPO and Ethyl cellulose individually and in combination of abovenpolymers.Matrix tablets assessed for their physicochemical properties and invitro drug release studies. *Invitro* release data shows individual low polymer concentration of RLPO, RSPO sustain the drug release up to 10hrs but combinations with EC sustain the drug release more than 12h.Eudragits in higher polymer proportion drug release was extend up to 12h. Ethyl cellulose has more retardation than Eudragits. Analysis of the release kinetics indicated that drug release mechanism was fickian diffusion.[60]

Huyen Thi Than et el (2011)., developed the sustained release (SR) tablets containing solid dispersions (SD) granules of a poorly water-soluble drug were prepared to investigate the controlled pH-independent release of the drug. Poloxamer 188 was used as an SD carrier. The SD granules dissolved completely within 10 min, a dissolution rate much higher than that of pure LST. Moreover, pH-independent sustained release of LST from the SD-SR tablet was achieved for 2 h in gastric fluid (pH 1.2) and for 10 h in intestinal fluid (pH 6.8). A combination of SD techniques using surface adsorption and SR concepts is a promising approachto control the release rate of poorly water-soluble drugs in a pH-independent manner.[61]

Shady M.Abed EL-Hali et al (2011)., designed oral controlled-release matrix tablets of SS using hydrophilic polymers. The effects of polymer concentration, polymer viscosity and binary mixtures of some polymers on the *invitro* drug release were studied.

The different prepared tablet formulae exhibited content uniformity within the acceptable limit and showed good mechanical properties. Increasing the polymer concentration from 25% to 60%, as well as increasing HPMC viscosity resulted in significant retardation (p<0.05) of the drug release. The matrix tablets formulated using HPMC K100M and guar gum in a ratio of 1:1 succeeded to control drug release up to 80.8% in 12 h.[62]

Viena D.Dias et al (2007)., developed and designed the suitability of a hypromellose (HPMC) matrix system to achieve a bi-phasic releasebprofile: a fast release within 15 minutes (similar to an immediate release preparation) followed by extended drug release, using conventional tableting and coating technologies. In addition, the influence of a color top coat on drug release was investigated. Zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class was selected as the model drug.[63]

A.K.Singhai et al (2011)., desinged and developed the controlled release (CR) matrix tablets of rifampicin by using Hydroxypropyl methylcellulose (HPMC) polymer (medium and high viscosity) by direct compression method. Influence of formulation variables such as drug: HPMC ratio, viscosity grade of HPMC on the formulation characters and drug release has been studied. The results indicated that the release rate of the drug and the mechanism of release from the HPMC matrices are mainly controlled by the drug: HPMC ratio and viscosity grade of the HPMC. The formulations were found to be stable and reproducible.[64]

Hiremath PS et al(2008)., carried out oral matrix tablet formulations for controlled release of anti-tubercular drugs like rifampicin, isoniazid using polymers HPMC, HPC(hydroxyl propyl cellulose) and Eudragit L100**.** They found that the proper combination of non-ionic and anionic polymers and a careful selection of formulation and process parameters could provide controlled release of rifampicin and isoniazid from a single matrix tablet. From their studies it was observed that the controlled release formulations containing 80% HPC and 60% Eudragit found to provide required release profile for both rifampicin and isoniazid. Thus, the optimized formulation of the present study provided both required initial release for rifampicin (80–100 mg) and isoniazid (36% of the dose) as loading dose and controlled release of rifampicin and isoniazid as maintenance dose from a single controlled release matrix tablet.[65]

Hiremath PS et al (2008)., studied oral controlled release formulations of rifampicin and effect of formulation variables and process parameters on *invitro* release. The effect of HPMC viscosity, HPMC ratio, and rifampicin particle size on the release of rifampicin from CR matrix tablets. The above results indicated that the release rate of the drug and the mechanism of release were mainly controlled by the polymer viscosity/molecular weight and polymer ratio. The drug release could be extended from 12h to beyond 24h by varying polymer ratio and viscosity character of the polymer.[66]

3.1 AIM OF THE WORK

Glucosamine is an amino monosaccharide which is used for the treatment of osteoarthritis. Glucosamine is an essential component of mucopolysaccharides and chitin. Mucopolysaccharides (glycosaminoglycons) are large complexes of negatively charged carbohydrate chains that are incorporated into mucous secretions, connective tissue, skin, tendons, ligaments and cartilage.

Glucosamine was administered orally as a Glucosamine salt get absorbed from the small intestine and it is transported via the portal circulation to the liver. Glucosamine is catabolized by first-pass metabolism in the liver and also by the gut metabolism. So to avoid this, Glucosamine has been taken in high dose to attain better bioavailability. An ingested tablet taken by the people for a long term, the major side effect suffered by the patients was tachycardia due to more concentration of drug in blood. Hence the present study is to release the drug in a required quantity to the body for that we planned to develop a sustained release formulation of Glucosamine hydrochloride.

The success of a therapy depends on selection of the appropriate delivery system as much as it. Depends on the drug, sustained release dosage form are designed to complement the pharmaceutical activity of the medicament in order to achieve the better selectivity and longer duration of action.

The aim of this present work is to formulate a Glucosamine Hydrochloride 1500mg Sustained release matrix tablet by wet granulation method using polymers such as hydroxyl propyl methyl cellulose K100M and K200M, ethyl cellulose. The best formulation is to be selected on the basis of evaluation characteristics.

To increase the residence time of the drug in the intestine and release the drug for a sustained period of time with following objectives;

- Improve patient compliance.
- Reduce dosing frequency.
- Increase bioavailability of the drug.
- To improve the efficacy of drug treatment.

3.2 PLAN OF WORK

The present work was carried out to prepare Glucosamine Hydrochloride sustained release tablets and evaluate the *invitro* release of drug from the tablets. The stages involved in the plan of work are as follows.

1. Construction of standard curve
2. Compatibility study between drug and selected polymers.
    - By Fourier Transform Infrared Spectroscopy.
3. Formulation of sustained release tablets
4. Evaluation of formulated tablets
    a) Physical parameters like thickness, weight variation, friability and hardness
    b) *Invitro* drug release
    c) Drug content uniformity
    d) Selection of best formulations.
    e) Stability Studies
    f) Data analysis (drug release kinetics)

Table no: 2

MATERIALS AND METHODS

S.No	Ingredients	Manufacturer/Vendor
1	Glucosamine Hydrochloride USP (ASMF grade)	Hygia health co ltd.,Mumbai
2	Calcium Hydrogen Phosphate Anhydrous BP/Ph.Eur	Enarchemi Private limited,Goa
3	Hypromellose K200M BP/Ph.Eur	Aqualon, Mumbai
4	Ethocel 100 cps FP BP/Ph.Eur	Dow Chemicals, Bangalore
5	Sodium Alginate (NS Enteric)	Dow Chemicals, Bangalore
6	Povidone BP/Ph.Eur K90F	ISP International specialty products, Mumbai
7	Hypromellose K100M BP/Ph.Eur	Dow chemicals,Mumbai
8	Microcrystalline Cellulose BP/ Ph.Eur PH102	FMC Biopolymer,Bangalore
9	Colloidal anhydrous silica BP/Ph.Eur	Cabot Sanmar Pvt. Limited., Mumbai
10	Stearic acid BP/Ph.Eur (50)	Taurus chemicals (P) ltd.,Ahmedabad
11	HypromelloseBP/Ph.Eur (HPMC E-5)	Dow chemicals ,Bangalore
12	Macrogol BP/Ph.Eur PEG 6000	Manali petro chemicals Viswaat chemicals India glycols limited,Goa
13	Opadry white IH OY-58900	Colorcon Asia Pvt.Ltd.Goa
14	Isopropyl alcohol BP/Ph.Eur	Exxon/ Lee changyung Deepak fertilizers,Goa

Table no: 3

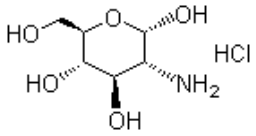
INSTRUMENTS AND EQUIPMENTS

S.No.	Name of Instrument	Manufacturer
1	Digital Weighing balance	Essaedigi,Germany
2	Vibratory Sifter	Ganson / Anchor, Bombay
3	Multimill	Ganson / Anchor, Mumbai
4	Rapid high shear mixer granulator	Ganson,Mumbai
5	Fluid Bed Drier	Bectochem,Germany
6	Octagonal Blender	Ganson / Bectochem,Japan
7	Tablet Compression machine	Cadmach Machinery pvt. Ltd,Mumbai
8	Vernier calipers	Mitatoyo.China
9	Friability apparatus	Electrolab,Mumbai
10	Hardness tester	Varian,China
11	Moisture balance	EssaeTeroka,Mumbai
12	Autocoater	Neocota,Goa
13	Digital pH meter	Ecoscan,China
13	Six station dissolution test apparatus	Electro Lab, Lab India, Mumbai
14	UV-Visible Spectrophotometer	Shimadzu,Japan
15	Stability chamber	Osworld,Mumbai
16	Sonicator	Santorious flexit,Germany
17	Bulk density apparatus	Campbell electronics,Mumbai

4.3 Drug profile:- [67,68,69,70]

Glucosamine Hydrochloride:-

Table no:4 Physico-Chemical characterizations

S. No	Parameter	Observation
1	**Description**	White crystalline with odorless, slight sweet.
2	**Structure**	
3	**Molecular formula**	$C_6H_{13}NO_5 \cdot HCl$
4	**IUPAC Name**	2-Amino-2-deoxy-D-glucopyranose hydrochloride (D-Glucose, 2-amino-2-Deoxy-, hydrochloride.)
5	**Molecular weight**	215.63
6	**Category**	Osteoarthritis, Muscle Injury Prevention, Osteochondritis; Rheumatoid Arthritis, tendonitis
7	**Solubility**	Soluble in water, but insoluble in organic solvent such as ethanol and faintly soluble in methanol.
8	**Melting point**	190-to194 ℃
9	**Half-life**	(1.09 ± 0.98 h)

Description: -

Glucosamine Hydrochloride is an amino sugar and a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids. A type of Glucosamine forms chitin, which composes the exoskeletons of crustaceans and other arthropods, cell walls in fungi and many higher organisms. Glucosamine is one of the most abundant monosaccharide. It is produced commercially by the hydrolysis of crustacean exoskeletons. Glucosamine is commonly used as a treatment for osteoarthritis, although its acceptance as a medical therapy varies.

Bioavailability and Pharmacokinetic data:-

Glucosamine is rapidly absorbed, highly distributed and efficiently cleared. Since the low bioavailability of the drug is evident only after oral administration, the gut rather than liver is implicated for an apparent large first-pass effect.

After intravenous administration, the apparent terminal half-life (1.09 ± 0.98 h), apparent steady state volume of distribution (2.1 ± 1.1 $L.kg^{-1}$) and total body clearance (2.61 ± 0.81 $L.kg^{-1.h-1}$) were calculated. The peak plasma concentration, after oral administration, occurred approximately 30 min post-dose and the absolute bioavailability was 0.19. Glucosamine was completely bioavailable after intraperitoneal administration.

Absorption:-

Glucosamine undergoes a rapid oral absorption. The absolute bioavailability of the drug by oral route was only 26% due to first-pass hepatic metabolism.

Distribution:-

Glucosamine is not a protein bound but rather incorporates into plasma proteins (primarily globulins).The volume of distribution (Vd) of the drug was 2.5 lts.

Metabolism:-

Glucosamine hydrochloride is rapidly absorbed by oral or parenteral administration. It is metabolized (predominantly in the liver) to smaller molecules and ultimately to carbon dioxide, water and urea.

Excretion:-

Scientific evidence for the safe use of glucosamine hydrochloride during lactation is not available. Approximately 11% of an orally administered dose of radio-labelled glucosamine HCL was excreted in the feces; most of this appears to be unabsorbed drug. Less than 1% of radioactivity after radio-labeled intravenous or intramuscular doses appears in the feces.

Mechanism of action:

The Precursor Supply Theory is the most popular explanation regarding the apparent beneficial effects of Glucosamine hydrochloride in Osteoarthritis. This theory states that Glucosamine hydrochloride supplies excess basic building blocks for the synthesis of cartilage glycosaminoglycans and/or bypasses rate-limiting steps in glycosaminoglycans synthesis.This is clinically relevant because it predicts that the non-sulfated salts of Glucosamine (i.e., Glucosamine hydrochloride and *N*-acetyl Glucosamine) will be ineffective.

As a result of extensive *invitro* testing, it is postulated that one or more alternate mechanism of action for Glucosamine hydrochloride in Osteoarthritis may include:

- Squelching small signaling molecules such as Nitrous oxide and oxygen radicals that can damage articular cartilage.
- Exerting anti-inflammatory properties by decreasing prostaglandin E2 (PGE2) levels through suppression of cyclo-oxygenase-2 (COX-2) gene transcription16 or by increasing the production of hyaluronic acid in synovial fluid.
- Mediating aggrecanase degradation of articular cartilage.
- Exerting anticatabolic effects by decreasing expression, synthesis, or activity of matrix metalloproteinase's (MMPs).

Since the exact mechanism(s) of Glucosamine hydrochloride on cartilage metabolism remain to be elucidated and because high *invitro* doses are being used to study Glucosamine, extrapolation of findings to the *invivo* setting must be done with caution.

ADVERSE EFFECTS:

In rare instances, some gastric discomfort was reported but was easily relieved by taking the supplement with food.

DRUG INTERACTIONS:-

Glucosamine did not affect hemoglobin in a randomized, double-blind, placebo-controlled trial of 34 patients with well-controlled type 2 diabetes mellitus. The results of this trial may not apply to patients with uncontrolled diabetes .Glucosamine is likely safe for patients with diabetes that is well-controlled with it only or with one or two oral antidiabetic agents

DOSE:

Most studies use 1500-2000 mg per day. 1500 mg per day is the most common dose. Dosages in the 3000 mg per day range have been used safely. Maintenance doses of 750 to 1500 mg per day have been used. We recommend starting with 3000 mg per day of the Glucosamine capsules or powder for 1-3 months until some relief of pain has begun, then taper the dose down by 500-1000 mg per day until a maintenance dose is achieved between 1000 and 1500 mg per day. The 1000 mg capsules allow for a single daily dose in those who have achieved their level of maintenance pain relief.

DOSAGE FORM: Tablet, Capsules, Oral powders, Ointments and Oral Liquids

4.4 EXCIPIENTS PROFILE[71,72]

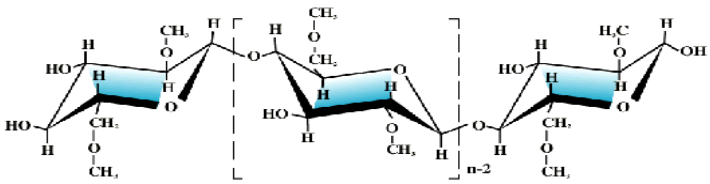
1. HYPROMELLOSE

Non-proprietary name: Hypromellose, Hydroxypropylmethyl cellulose, Hypromellose.

Synonyms: Benecel MHPC, E464 Hydroxypropylmethyl cellulose HPMC, Cellulose Hydroxypropylmethyl ether

Chemical name: Cellulose Hydroxypropyl methyl ether.

Structural formula:



Molecular weight: 10,000 – 1,500,000.

Functional category: Film former, Rate controlling polymer for sustained release, Viscosity – increasing agent.

Pharmacopoeia: BP, Eur. Pharmacopoeia, and USP.

Description: Odorless, tasteless, White or creamy white colored, fluffy, acid, hygroscopic powders with slight characteristics odor.

Aqueous viscosity: Methocel K100M: 1, 00,000 mPas.

Solubility: Soluble in cold water forming viscous colloidal solution.

Stability and storage condition: Stable at room temperature should be store in airtight container in a cool and dry place.

Incompatibilities: Hypromellose are incompatible with some oxidizing agents.

Application: It's used in oral ophthalmic and topical preparations. They are mainly used as the matrix in sustained release formulation

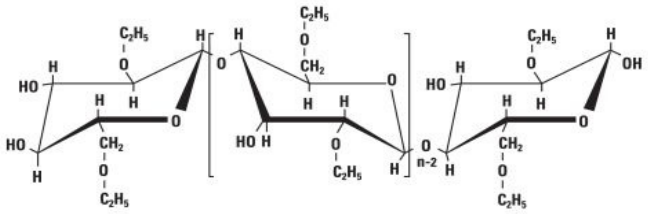
2. ETHYL CELLULOSE

Non proprietary name: Ethyl cellulose, Ethyl cellulose.

Synonyms: Aqua coat ECD, Aqualon E462, Ethocel, surelease.

Chemical name: Cellulose ethyl ether.

Structural formula:



Functional category: Coating agent, flavoring fixative, tablet binder, tablet filler, Viscosity- increasing agent.

Pharmacopoeia: Ph.Eur. BP and USP.

Description: Tasteless, free-flowing, white to light tan-colored powder.

Viscosity: EthocelStd 100 FP: 90-110 mPas.

Solubility: Freely soluble in chloroform, methyl acetate, and tetrahydrofuran, partially soluble in water.

Storage condition: It's stable but slightly hygroscopic in nature. Ethyl cellulose are stored at temperature not exceed 32 ^{o}c in dry area away from all sources of heat.

Application: Mainly used as a matrix forming material in sustained release formulation. It's also used as a film forming controlling releasing agent in coating.

USES:

Use	Concentration (%)
Microencapsulation	10.0–20.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

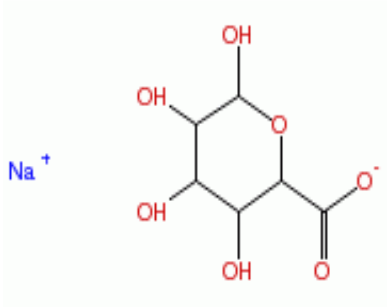
3. SODIUM CARBONATE

Non proprietary name: Sodium Alginate

Synonyms: Alginatesodico; align; alginic acid, sodium salt; E401; Kelcosol; Keltone; natriialginas; Protanal; sodium polymannuronate.

Chemical name: Sodium alginate

Structural formula:



Functional category: Stabilizing agent; suspending agent; tablet and capsule Disintegrant, Tablet binder; viscosity increasing agent.

Pharmacopoeia: Ph.Eur. BP and USP.

Description: Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Viscosity: A 1% w/v aqueous solution, at 208C, will have a viscosity of 20–400 mPas

Solubility: Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Slowly soluble in water, forming a viscous colloidal Solution

Storage condition: Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature.

Application: It is mostly used as Disintegrant and binder in tablet formulation. Diluents in capsule formation, preparation of sustained –release oral formulation it will delay the dissolution of the drug, thickening and suspending agent in gels, cream

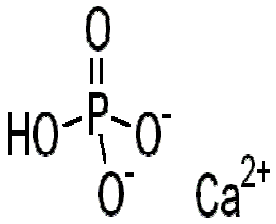
4. ANHYDROUS CALCIUM HYDROGEN PHOSPHATE

Non proprietary name: Anhydrous calcium hydrogen phosphate, anhydrous dibasic calcium phosphate, Calcium hydrogen phosphate anhydrous, Dibasic calcium phosphate.

Synonyms: A-TAB; calcium monohydrate phosphate; calcium orthophosphate; Di-Cafos AN; Dicalcium orthophosphate; E341; Emcompress Anhydrous; Fujicalin.

Chemical name: Dibasic calcium phosphate

Structural formula:



Molecular weight: 136.06

Functional category: Tablet and capsule Diluents.

Pharmacopoeia: BP, Eur. Pharmacopoeia, JP and USPNF.

Description: Anhydrous dibasic calcium phosphate is a white, odorless, tasteless Powder or crystalline solid. It occurs as triclinic crystals

Solubility: Practically insoluble in ether, ethanol, and water; Soluble in dilute acids.

Stability and storage condition: Dibasic calcium phosphate anhydrous is a nonhygroscopic, relatively stable material. Under conditions of high humidity it does not hydrate to form the dehydrate.

Incompatibilities: Calcium hydrogen phosphate is incompatible with tetracycline antibiotics.

Application: Dibasic calcium phosphate anhydrous is widely used in oral pharmaceutical products, food products, and toothpastes, dentifrice formulation also used as abrasive and lubricant.

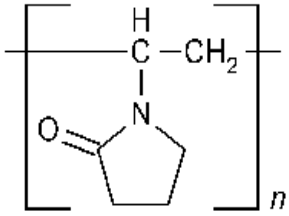
5. POVIDONE

Non proprietary name: povidone, povidonum.

Synonyms: E1201, Kollidon, plasodone, Polyvidon, Polyvinylpyrrolidone, pvp.

Chemical name: 1- ethenyl-2-pyrrolidione homopolymer.

Structural formula:



Molecular weight: 2500 – 3,000,000.

Functional category: Disintegrant, dissolution aid, suspending agent and tablet binder.

Pharmacopoeia: BP, Eur. Pharmacopoeia, JP and USP.

Description: Fine, white to creamy – white colored, odorless hygroscopic powder.

Aqueous viscosity: Povidone K90 - 53.0(ethanol): 90.0(propon-2-ol) in 5%w/v.

Solubility: Freely soluble in acids chloroform, ethanol and water but insoluble ether and mineral oils.

Stability and storage condition: Stable to heat exposure around 110 -130'c, steam sterilization of the aqueous solution does not alter its properties. Should be store in well-closed container, in a cool and dry place.

Incompatibilities: Incompatible with some inorganic salts, natural and synthetic resins and other chemicals. Preservative like thimerosal may forms complex with Povidone.

Application: Povidone is widely used as a binder in wet granulation, solubizing agent in oral or parenteral preparation, suspending, stabilizing and viscosity-increasing agent.

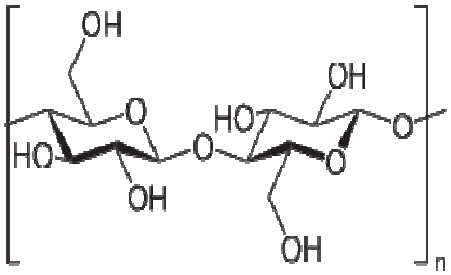
6. MICROCRYSTALLINE CELLULOSE

Non proprietary name: Microcrystalline Cellulose, Microcrystalline Cellulose Cellulose, Microcrystalline Cellulose

Synonyms: Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur..

Chemical name: Cellulose.

Structural formula:



Molecular weight: 36 000.

Functional category: Adsorbent; suspending agent; tablet and capsule Diluents; tablet disintegrate.

Pharmacopoeia: BP, Eur. Pharmacopoeia, JP and USP, NF.

Description: Purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Stability and storage condition: Microcrystalline cellulose is a stable though hygroscopic material. .The bulk material should be stored in a well-closed container in a cool, dry place

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents

Safety: It is generally regarded as a nontoxic and non-irritant material, having little toxic potency. In deliberate abuse formulation has result in cellulose granulomas.

Application: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/Diluents in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its used as a binder/Diluents', microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

7. COLLOIDAL SILICON DIOXIDE

Non proprietary name: Colloidal Anhydrous Silica Light Anhydrous Silica Acid Silica, Colloidal Anhydrous Colloidal Silicon Dioxide

Synonyms: Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; fumed silicon dioxide; hochdispersessilicumdioxid; SAS; silica colloidalisanhydrica; silica sol; silicianhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica; Wacker HDK.

Chemical name: Silica

Structural formula: SiO_2

Molecular weight: 60.08

Functional category: Adsorbent; Anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet Disintegrant; thermal stabilizer; viscosity-increasing agent.

Pharmacopoeia: BP, Eur. Pharmacopoeia, JP and USP, NF.

Description: Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Form a colloidal dispersion with water. For aerosil, solubility in water is 150 mg/L at 258C (pH 7).

Stability and storage condition:-Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying should be stored in a well-closed container

Incompatibilities: Incompatible with diethylstilbestrol preparations.

Safety: It is generally regarded as a nontoxic and non-irritant material; however, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

Application

- Colloidal silicon dioxide is widely used in pharmaceutical industries, food products, and in cosmetics.
- Helps in increase the flow properties of the dry power.
- Used as stabilizer in suspension, thixotropic thickening and suspending agent in gels.
- Also used as tablet disintegrate, and as adsorbent in wax micro spheres.

8. STEARIC ACID

Non proprietary name: Stearic acid, Acidumstearium.

Synonyms: Cethlacetic acid, crodacid E570, Edenor, Emersol, Hystrene, Kortacid 1895.

Chemical name: Octadecanoic acid.

Structural formula:

Molecular weight: 284.47 (for pure material)

Functional category: Emulsifying agent, solubizing agent, Tablet and capsule lubricant.

Pharmacopoeia: BP, Eur. Pharmacopoeia, JP and USPNF.

Description: Hard, white or faintly yellow – colored, somewhat glossy, crystalline solid or white or yellowish white powder with slight odor and taste suggesting tallow.

Solubility: Freely soluble in benzene, carbon tetrachloride, chloroform and ether also insoluble in water.

Stability and storage condition: It is a stable material but in case of bulk materials some antioxidant may be used. Should be stored in a well closed container and kept in a cool and dry place.

Incompatibilities: Stearic acid is incompatible with most metal hydroxides and oxidizing agents.

Application: Stearic acid is widely used in oral and topical pharmaceutical formulation. It has also been mainly used in oral preparation of tablets or capsule as lubrication and also as a binder. It's also used in cosmetic and food products.

5.1 Construction of Standard curve of Glucosamine Hydrochloride:-

Dervitization of Glucosamine Hydrochloride: [73, 74]

0.2 M Borate buffer:

About 7.63 g of sodium borate was weighed and transferred into a 100ml volumetric flask containing 80 ml of distilled water, adjust to a pH of 9.5 with hydrochloric acid and volume was made upto 100ml with solvent and mixed well.

Derivitizing reagent:

About 0.2g of o-phthalaldehyde was weighed and transferred into a 100ml volumetric flask, dissolved in 5 ml of anhydrous methanol sonicated for 10 minutes to this 0.2ml of 3-mercaptopropionic acid and 45 ml of 0.2 M Borate buffer was added and mixed gently, volume was made upto 100ml. The reagent was placed in the dark for 30minutes before using.

Procedure:-

a) Preparation of primary stock solution:-

About 150mg of drug was weighed and transferred into a 100ml volumetric flask containing distilled water and volume was made upto 100ml from that 2 ml was pipetted out and transferred into 50ml volumetric flask and volume was made upto 50ml with distilled water.

b) Preparation of secondary stock solution:-

From the primary stock solution 5ml was pipetted out and transferred to a 20ml volumetric flask, to this 2ml of derivatizing reagent was added and volume was made upto 20ml with distilled water .

5.1.4. Standard spectrum of Glucosamine Hydrochloride SR tablets[75]

About 150mg of drug was weighed and transferred into a 100ml volumetric flask, volume was made upto 100ml with distilled water from this solution 2 ml was pipetted out into a 50ml volumetric flask, volume was made upto 50ml again from this solution 5ml was pipetted out and transferred into a 20ml volumetric flask to this add 2 ml of derivatizing reagent and volume was made upto 20ml with distilled water. The spectrum was taken in the range of 200 to 400 nm. The λmax was found to be 205nm.

5.1.5. Standard curve of Glucosamine hydrochloride:-[75]

Standard curve of Glucosamine hydrochloride was carried out by using the different concentrations. 100 mg of drug was dissolved in 100 ml of distilled water and from that, further dilution was made in different concentration of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml, 30µg/ml .Their absorbance are observed at 205 nm using derivatizing reagent and the graph has been plotted between Absorbance Vs Concentration.

A standard graph was plotted by keeping the known concentration on x-axis and obtained absorbance on y-axis.

Table no: 5 Data for Standard curve

Standard curve of Glucosamine hydrochloride SR Tablets	
Concentration(µg/ml)	**Absorbance**
5	0.156
10	0.321
15	0.468
20	0.624
25	0.779
30	0.936

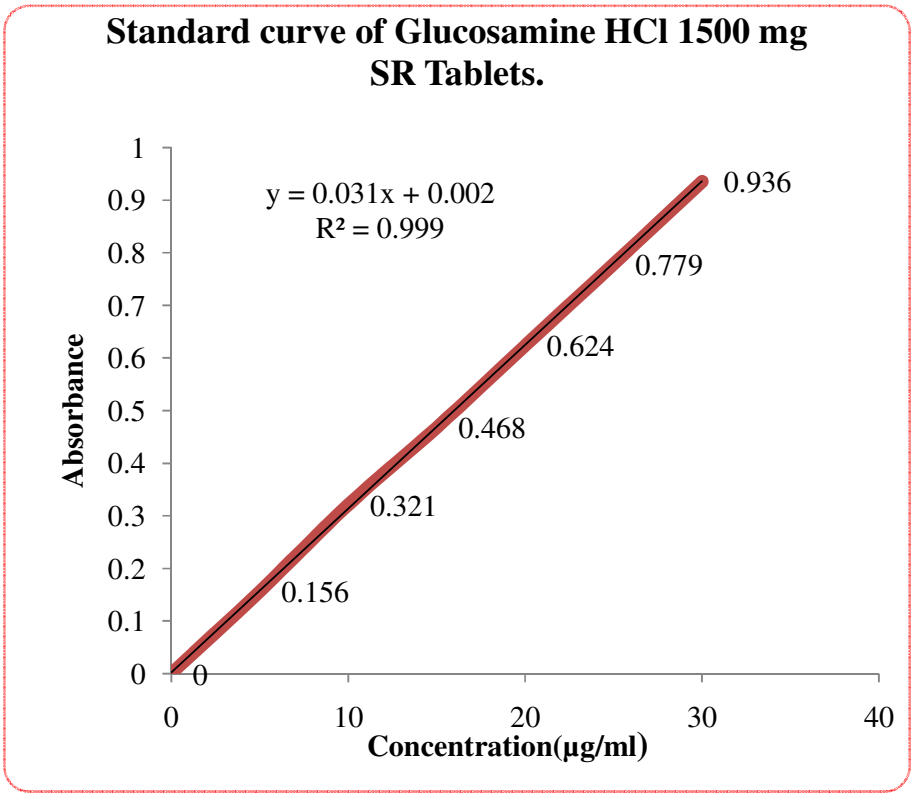


Fig no:3

5.2 Preformulation studies:-[76]

Preformulation studies can be defined as an investigation of physical and chemical properties of active pharmaceutical ingredient, alone and in combination with excipients. The objective of Preformulation studies is to generate information useful to the formulator in developing stable and bioequivalent dosage form that can be mass- produced.

- Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms.
- The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.
- The use of preformulation parameters maximizes the changes in formulating an acceptable, safe, efficacious and stable product.

- The drug (Glucosamine Hydrochloride) in powder form and granules were subjected to the following physical test for 3 times and average values were noted.

5.2.1Derived properties:-[76]

a) Bulk density:- Bulk density is defined as a mass of a powder divided by the bulk volume.

A sample powder of Glucosamine Hydrochloride (10 g) was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by the formula given below;

$$\text{Bulk density } (\rho_0) = M/Vo$$

Where, M = mass of the powder

Vo = volume of the powder

b) Tapped Density:-

The powdered sample was screened through sieve no: 18 and the weight of sample equivalent to 10 g were filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out at a rate of 300 drops per minute for 500 times from 3" height and the tapped volume Vf was noted. The tapped density was calculated in gm/ cm^3 by the formula,

$$\text{Tapped density } (\rho_t) = M/Vf$$

Where, M = weight of sample powder taken

Vf = tapped volume

c) Compressibility Index:

The bulk density and tapped density was measured and compressibility index was calculated using the formula,

$$C.I. = \{(\rho_t - \rho o)/\rho t\} \times 100$$

Where,

ρt = tapped density

ρo = bulk density

d) Hausner's ratio:

Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula,

$$\text{Hausner's ratio} = \rho t/\rho$$

Where,

ρt = tapped density

ρo = bulk density

5.2.2 Infrared Spectroscopic studies:-[74]

Identification of the pure drug and polymer were performed using infrared spectroscopy.

IR spectroscopy (using Perkin Elmer) by KBr pellet method was carried out on drug and polymer. They are compressed under 10 tones pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000 to 400cm-1 in a spectrophotometer and peaks obtained were identified.

5.2.3Drug Excipient compatibility studies:-

Binary mixtures of drug and excipients in the ratio 1:1 by trituration were prepared and packed in glass vials. All the samples were kept in 40°C/75%RH storage conditions for 1 month. The samples were observed for color change at a frequency of 7 days for a period of one month.

- The drug and the excipients were also mixed in 1: 1 ratios and was kept in **40°C/75% RH** for 1 month
- The drug and the excipients were triturated with IPA as granulation solvents kept in **40°C/75% RH** for period of 1 month.

Compatible Excipients:

Based on the drug: excipients compatibility study, the following excipients were considered as compatible and used in the present product development.

- Dicalcium phosphate anhydrous (DC grade ,unmilled , A-TAB)
- Ethyl Cellulose.
- Stearic Acid (Powder)

- Isopropyl Alcohol
- Microcrystalline Cellulose.
- Opadry white OY 58900
- Opadry white OY 85f18422
- Colloidal anhydrous silica
- HPMC K100M and K200M.

5.3 Formulation of Glucosamine hydrochloride:-

Glucosamine hydrochloride sustained release tablets were prepared by using wet granulation method. The hydoxy propyl methyl cellulose, calcium hydrogen phosphate anhydrous, microcrystalline cellulose powder, active ingredient and povidone k90 solution are mixed homogeneously. Like that hypromellose K200M was used instead of K100M for another batches. The blend was placed in the rapid mixing granulator inorder to prepare the granules and then dried in the fluidized bed dryer at a temperature of 55^0C.The granules are passed #20mesh, stearic acid was added as a lubricant. The dried granules were compressed in 27 stationary double rotary punching machine into tablets by using 22x11mm oval shaped punch.

5.3.1 Design and composition of formula:-[77]

The design of tablets is an important part of the formulator, to produce a product with desired properties. It involves the correct selection and balance of excipient for active ingredients to achieve the desired response.

Based on primary information on the uncoated and coated tablets and previous experience with the manufacturing of various products, the following tentative product specifications were proposed before starting the formulation trials.

5.3.2Justification for the design of the composition:

In addition to the active, Glucosamine Hydrochloride 1500mg SR tablets contained a number of inert materials as diluents, binders, glidant, lubricants and coating polymers to impart satisfactory processing, compression and release characteristics to the formulation. The justification for the inclusion of these functional additives is briefly described below:

a. Diluents:

They are inert materials added to increase the bulk in order to make the tablet with a desired particle size for compression. Calcium Phosphate anhydrous, Microcrystalline Cellulose was used in the present development as directly compressible materials.

b. Binders:

Materials used to impart cohesive quality to the powdered materials are referred to as binders. They impart cohesiveness to the tablet formulation which ensures the tablet remaining intact after compression as well as improving the free flowing qualities by the formulation of granules of desired hardness and size. In the present study Povidone K 90 was selected as binder.

c. Lubricants:

They prevent the adhesion of the tablet material to the surface of the dies and punches reducing inter-particle friction, facilitating the ejection of the tablet from the die cavity and improve the rate of flow of the tablet granulation.

Stearic acid was used as lubricant which is in hydrophobic in nature and it is a proper choice as the tablet does not shows any tendency to stick to the side of the die. The tablets were found to be satisfactory and the dissolution profile of the drug substance was satisfactory with the use of Stearic acid.

d. Coating formula components:

The core tablets were coated with a film coating consisting of the film formers Opadry WhiteOY 58900, HPMC E-5 and PEG 6000 as processing aid.

Table no: 6 Formulation Details

Inactive Ingredient	Category	Concentration per tablet
Core Ingredients		
Calcium hydrogen phosphate anhydrous	Diluent	2-4%
Povidone K90F	Binder	2-3%
Hypromellose K200M	Polymer	2.55%
Hypromellose K100M	Polymer	5-8%
Micro Crystalline Cellulose	Diluent	2-5%
Colloidal silicon dioxide	Glidant	0.27-0.97%
Stearic Acid	Lubricant	1.08-2.16%
Coating Ingredients		
Opadry White OY 58900	Color	0.59%
Opadry white OY 85f18422	Color	0.48-0.59%
Hypromellose E-15	Thickener	0.052-0.27%
Propylene glycol	Plasticizer	Qs
Isopropyl Alcohol	Solvent	Qs
Purified Water	Solvent	Qs

5.3.3 Manufacturing procedure for Glucosamine hydrochloride SR tablets:-[78]

Step 1: Dispensing: All the materials are dispensed.

Step 2: Sifting:

a) The materials Glucosamine Hydrochloride, Hypromellose K 200M, was sifted through #40 mesh and collected separately into polyethylene bags.
b) The extra granular materials like Glucosamine Hydrochloride, Hypromellose K 200M, Colloidal Anhydrous Silica was sifted through # 40 mesh and collected separately in double lined poly bag.
c) The stearic acid was sifted through # 40 mesh and collected separately in a double lined polybag.

Step 3: Binder solution preparation:

The required quantity of purified water was taken into a suitable stainless steel vessel and required quantity of Povidone k 90 F was added (Binding solution) and stirred well by using magnetic stirrrer. The stirring was continued until the clear solution was formed.

Step 4: Granulation:

The presifted materials of STEP 2(a) was loaded into a rapid mixing granulator and mixed for 5 minutes with impeller at slow speed.

Step 5: **Binder addition**:

The binder solution was added to step 3 gradually to the dry mix for 1 – 5 minutes with impeller at slow speed.

Step 6: **Kneading:**

After complete addition of binder, the mixing was continued for 10 sec to 1 minute with impeller and chopper at high speed. The impeller and chopper were switched off. The granules were taken and visually observed for the consistency of the granules and the wet mass was loaded into the fluidized bed dryer bowl.

Step 7: Drying:-

The inlet temperature was set at 45°C (Limit: 40°C - 50°C) and the granules were dried for 10 minutes repeatedly until the moisture content reaches the limit.

Step 8:- Sifting and Milling:

1. The dried granules were sifted by using vibratory sifter fitted with #20 mesh and the retained granules are taken into a respective double lined polyethylene bags.
2. The retained granules are milled by using multi mill fitted with 1.5 mm screen in knives forward direction at medium speed and collected into a double polyethylene bag. The milled granules were passed through #20 mesh, again the retained granules are milled through 1.0mm screen. Then the milled granules are passed through #20 mesh and collected in a double lined polyethylene bags.

STEP 9: Blending:

The sized granules and the sifted extra granular materials Glucosamine Hydrochloride (part II), Hypromellose K100M, Microcrystalline Cellulose pH102 and Colloidal anhydrous silica are loaded into a octagonal blender and blended for 10 minutes.

STEP 10: Lubrication:

Sifted Stearic acid was loaded into the blender and blended for 5 minutes

STEP 11: Compression:

Lubricated blend was compressed in 22x11 mm oval shaped bevel ledge punch with average weight of 1985mg.

Table no: 7 Formulation composition (in mg)

Formula composition											
S.No	Ingredients	Batch no:									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	Dry mix										
1	Glucosamine hydrochloride	1500	1500	900	1500	900	900	900	900	900	900
2	Ethyl cellulose 45cps	115	90	-	-	-	-	-	-	-	-
3	Hypromellose K100M	100	100	-	-	-	-	-	-	-	-
4	Di-Calcium phosphate anhydrous	90	115	62	27	27	-	60	40	-	-
5	HypromelloseK200M	-	-	40	40	40	123	162	40	200	300
6	Ethyl cellulose100cps	-	-	-	55	55	82	-	-	-	-
	Binder										
7	PovidoneK30	20	20	-	-	-	-	-	-	-	-
8	PovidoneK90F	-	-	40	40	40	40	40	40	70	70
9	Purified water	qs	qs	-	-	qs	qs	qs	qs	qs	qs
10	Isopropyl alcohol	-	-	qs	qs	-	-	-	-	-	-
	Extra-granular										
11	Glucosamine hcl	-	-	600	-	600	600	600	600	600	600
12	HypromelloseK100M	-	-	80	-	-	110	-	100	-	-
13	HyprmelloseK200M	-	-	-	-	60	65	60	-	70	70
14	Microcrystalline cellulosePH102	-	-	83	83	83	-	60	70	-	-
15	Colloidal anhydrous silica	-	-	-	-	5	5	18	-	5	5
	Lubrication										
16	Stearic acid	-	-	40	40	40	20	18	20	40	40

Table no: 8 COATING COMPOSITION

S.No	Film coating (Layer I)	F6	F7	F8	F9	F10
1	Hypromellose(HPMC E-5)	-	-	9.00	9.00	9.00
2	PEG 6000(Macrogol)	-	-	1.00	1.00	1.00
3	Isopropyl alcohol	-	-	qs	qs	Qs
4	Purified water	-	-	qs	qs	Qs
	Film coating (Layer II)					
5	Opadry white OY-58900	25.00	-	11.00	-	-
6	Opadry white 85f18422	-	25.00	-	16	16
7	Purified water	qs	qs	qs	qs	Qs

***Invitro* Dissolution studies**:-[79]

Invitro drug release studies of Glucosamine Hydrochloride was studied by using dissolution apparatus USP typeII paddle method with a stirring speed of 50rpm at 37^0C ±0.5^0C in distilled water for 2 h and in 900ml of dissolution media. The samples were taken at preselected time intervals with replacement of equal volume of dissolution media. The collected samples were diluted and the absorbance was measured spectrophotometrically at 205nm.The percentage of Glucosamine Hydrochloride release at various time intervals were calculated from the standard graph.

5.4 Evaluation of Glucosamine Hydrochloride granules:-

All the formulated Sustained Release tablets were evaluated for following parameters

5.4.1 Content uniformity of dosage form by Mass variation method: [81]

The assay was carried out for the active substance(s) on a representative sample of the batch using an appropriate analytical method, this value was result A, expressed as percentage of label (as given below). Assumed that the concentration (mass of active substance per mass of dosage unit) was uniform.

Procedure:-

The 10 tablets were weighed individually. Calculated the active substance content, expressed as percentage of label claim, of each tablet from the mass of the individual tablets and the result of the assay, calculated the acceptance value.

5.4.2 Acceptance value:-[82]

Calculated the acceptance value (*AV*) as shown below, except that the individual contents of the units are replaced with the individual estimated contents defined below.

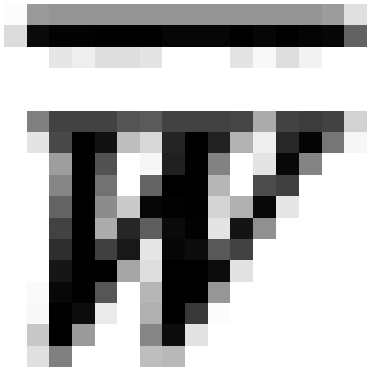
x_1, x_2... x_n = individual estimated contents of the dosage units tested,

where,

$$x_i = w_i \times \frac{A}{\overline{W}}$$

w_1, w_2... w_n = individual masses of the dosage units tested;

A = content of active substance (percentage of label claim) obtained using an appropriate analytical method (assay);



= mean of individual masses of the units used in the assay.

Calculation of Acceptance value:

Calculated the Acceptance Value (*AV*) using the formula

$$\left|M - \overline{X}\right| + ks$$

Acceptance Criteria:

(1) Acceptance value (AV) = **| M - X | + ks.**

Where,

k = Acceptability constant

If the number of tablets tested is 10, then k= 2.4

If the number of tablets tested is 30, then k= 2.0

s = Sample standard deviation.

(2) Calculated the mean of the individual contents (expressed as % of label claim) and note down as X.

(3) Determined the value of M as follows.

(i) If $98.5\% \leq X \leq 101.5\%$ then M = X

(ii) If $X < 98.5\%$ then M= 98.5%

(iii) If $X > 101.5\%$ then M = 101.5%

The requirements for dosage uniformity were met if the acceptance value of the first 10 dosage units is less than or equal to L1 (L1=15.0).

If the acceptance value is greater than L1, test additional 20 units and calculated the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1, and no individual content of any dosage units is less than Acceptance Value. L2 is 25.0.

5.4.1Evaluation of blend characteristics of Glucosamine Hydrochloride:-[83]

a) Angle of repose.

In order to determine the flow property, the Angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane.

$$\Theta = \tan^{-1} (h/r)$$

Where,

h=height,r=radius

Θ = Angle of repose

Procedure

- An accurately weighed sample was taken.
- A funnel was fixed in the stand in such a way that the tip of the funnel was at the height of 6 cm from the surface.

- The sample was passed through the funnel slowly to form a heap.
- The height and the circumference of the powder heap formed were measured.
- The radius was measured and the angle of repose was determined using the above formula. This was repeated five times for a sample

Table no: 9 Flow properties of powders and their angle of repose

Angle of repose in degree	Flow Property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

b) Determination if Bulk density and Tapped density:[83]

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm for duration 2 intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formula.

$$\text{Bulk density} = W / V_{O,}$$

$$\text{Tapped density} = W / V_f$$

Where,

W = weight of the powder,

V_O = initial volume,

V_f = final volume

c) Hausner's ratio:-[83]

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density

Table no:10 Flow property by Hausner's ratio

S.No	Hausner's Ratio	Property
1	0-1.2	Free flowing
2	1.2-1.6	Cohesive powder

d) Compressibility index (Carr's index).[83]

Compressibility index is an important measure that was obtained from the bulk and tapped density. In this theory, the less compressible material has the more flowable. A material having values of less than 20 to 30% was taken as the free flowing material.

$$\text{Carr's index} = \frac{\text{Tapped desnity} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table no: 11 Compressibility and flow property relationship

% Compressibility Index	Properties
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

5.5 Evaluation of Sustained release Tablets:-[83]

5.5.1 General Appearance:-

The general appearance of a tablet, its identity and general elegance was essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

5.5.2 Size & Shape:-

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness was measured by Vernier calliper or by other device. Tablet thickness should be controlled within a ± 7.5% variation of standard value.

5.5.3 Unique identification marking:-

These marking utilize some form of embossing, engraving or printing. These markings include company name or symbol, product code, product name etc.

5.5.4 Organoleptic properties:-

Color distribution must be uniform with no mottling. For visual color comparison compare the color of sample against standard color.

5.5.5 Hardness:-.

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength.

5.5.6 Friability:-

Friability of a tablet can be determined in laboratory by Roche friabilator. This consists of a plastic chamber that revolves at 25 rpm, dropping the tablets through a distance of Six inches in the friabilator, which is then rotated for 100 revolutions. The tablets are reweighed. Compressed tablet that lose weight should be less than 0.1 to 0.5 % of the tablet weight, which are considered as acceptable.

The percentage friability was measured using the formula,

$$\% F = \{1-(W / W_o)\} \times 100$$

Where,

% F = friability in percentage

W_o= Initial weight of tablet

W = Weight of tablets after revolution.

5.5.7 Weight variation test:-

About 20 tablets were weighed individually. Calculated average weight and compare with the individual tablet weight. The tablet pass the B.P. test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table no: 12 Weight Variation test as per BP.

Average weight of tablet	Maximum % difference allowed
80 mg or less	10
80 mg to 250 mg	7.5
More than 250 mg	5

% Maximum positive deviation = (W_H –A/ A) X 100

% Minimum negative deviation = (W_L - A / A) X 100

Where, W_H = Highest weight in mg.

W_L = Lowest weight in mg,

A = Average weight of tablet in mg

5.6 Stability studies:-[84]

Stability is defined as the extent to which a product retains the contents within specified limit and throughout its period of storage and use i.e. shelf life, the same properties that it possesses at the time of manufacture. These studies were designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

Stability studies are important to prevent the economic repercussions of marketing of an unstable product, since subsequent withdrawal and reformulation may lead to considerable financial loss. From the point of view of safety to patient, it is important that the patient receives a uniform dose of the drug throughout the shelf life of the product.

The International Conference on Harmonization (ICH) guidelines titled "Stability testing of new drug substances and products- Q1A (R2)" describes the stability test requirements for drug registration applications in the United States, European Union and Japan.

As per *in vitro* release formulation F_9 was found to be desirable than other formulations. Hence it was chosen for stability studies. The tablets were packed in 180cc HDPE(high deficiency polyethylene) bottles and kept for 3 months at different temperature 25°C / 60%RH, 30°C/ 75%RH, 40°C / 75% RH in a stability chamber (Osworld, Mumbai). At the interval of 1 month tablets were withdrawn and evaluated for physical properties like thickness, hardness, diameter, friability, weight variation, buoyancy studies and content uniformity. *In vitro* drug release is also carried out.

5.7 Kinetic Analysis of *InVitro* Release Rates of Sustained Release Tablets of Glucosamine hydrochloride: [77]

The results of in-vitro release studies obtained for all the formulations were subjected to graphical treatments to assess the kinetics of drug release.

Zero order Equation:

The results data was fitted into the Zero order equation.

$Q = K_0 t$

Q = The amount of drug released at time t

K_0 = Release rate

First order Equation:

The results data was fitted into the first order equation.

$\text{Log } C = \text{Log } C_0 - k\,t / 2.303$

C_0 – is the initial concentration of drug

K – is the first order constant

t - is the time.

Higuchi Model

Drug release for matrix devices by diffusion has been described by Higuchi classical diffusion equation

$$Q = \frac{[\, D\varepsilon \sqrt{(2A - \varepsilon Cst)}\,]}{\tau}$$

Where,

Q = Amount of drug released at time t

D = Diffusion coefficient of drug in tablet matrix

A = Total amount of drug in unit volume of tablet matrix

ε = Porosity of tablet

C_s = Solubility of drug in tablet matrix

t = Time in Min.

τ = Tortusity

The above equation can be simplified, if one assumes that D, ε, τ, Cs, and A are constants. Then equation can be written as

$$Q = Kt^{1/2}$$

When data is plotted according to the equation i.e. cumulative drug release versus square root of time, it yields a straight line, indicating that drug is released by diffusion mechanism. The slope is equal to K.

Peppa's Model

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following equation

$$\frac{Mt}{M\sigma} = Ktn$$

where,

M_t / M_σ = The fraction of drug released at time t.

K = Constant incorporating the structural and geometrical characteristics of the Drug / Polymer system.

n = Diffusion exponent related to mechanism of the release.

Above equation can be simplified by applying Log on both sides, we get.

$$Log\frac{Mt}{M\sigma} = LogK + n\,Logt$$

When the data is plotted as log of drug released versus log time, yield a straight line with a slope equal to n and k can be obtained from Y- intercept.

7. Results and Discussion

The present study was undertaken to formulate Glucosamine Hydrochloride sustained matrix tablets. Sustained release dosage forms deliver the drug at a slow release rate over an extended period of time. The drug Glucosamine Hydrochloride is formulated as a sustained release matrix tablet due to its high solubility in water and maintains required drug concentration in blood. So our aim of patient compliance was achieved.

Different grades of HPMC K100M and HPMC K200M were used as swellablepolymers, HPMC (hydroxyl propyl methyl cellulose) was chosen because it is widely used as a low density hydrocolloid system upon contact with water, a hydrogel layer would be formed to act as a gel boundary for the delivery system and it slowly release the drug as per sustained release concept and povidone K90 combination with HPMC (hyroxy propyl methyl cellulose) also has slow release property.

In the present study the 10 formulations were prepared by different polymers alone or in combination with diluents, the prepared formulations were evaluated for differentphysico chemical characteristics such as thickness, drug content, weight variation, hardness, and friability. The release characteristics of the formulation were studied in*invitro* conditions.

7.1. Preformulation studies:-

Based on preformulation data, Hypromellose K200M, Hypromellose K100M, Povidone K90 and Ethyl cellulose was taken as drug release retardants for formulation of SR matrix tablets of a highly water soluble drug.

Table no: 13Preformulation study data of the pure drug

S.No	Parameters	GlucosamineHydrochloride
1	Angle of repose	22.64 ± 0.002
2	Bulk density(gm/cm³)	0.66 ± 0.0124
3	Tapped density(gm/cm³)	0.84 ± 0.0047
4	Hausner ratio	1.24 ± 0.0081
5	Carr's index	27.16 ± 0.561
6	Loss on drying (%)	1.24 ± 0.008

- Values mentioned are average of 3 determinations

7.2. Characterization of Drug

7.2.1UV- Spectrum Analysis of Drug:-[75]

Glucosamine hydrochloride drug solution in distilled water was scanned using UV-Spectrophotometer between the range 200-400nm shown the maximum absorbance at 205nm.

7.3. Infrared spectroscopic study:-

By using FTIR technique Glucosamine hydrochlorideand polymers like hydroxy propyl methyl cellulose K100M and K200M were identified.

Table no:14Compatibility studies

Ingredients	Observations After 7 days	Observations After 14 days	Observations After 21 days	Observations After 30 days	Remarks
Glucosamine HCl	NCC	NCC	NCC	NCC	Compatible
Glucosamine HCl : IPA	NCC	NCC	NCC	NCC	Compatible
Glucosamine HCl: HPC	NCC	NCC	NCC	Slight color change	Can be used in the very small quantities
Glucosamine HCl: Colloidal anhydrous silica	NCC	NCC	NCC	NCC	Compatible
Glucosamine HCl: Stearic acid	NCC	NCC	NCC	Formation of flakes, no color change	Compatible
Glucosamine HCl: Magnesium stearate	NCC	NCC	NCC	NCC	Incompatible
Glucosamine HCl: PVP (K90)	NCC	NCC	NCC	NCC	Compatible
Glucosamine HCl: Ac-di-sol	NCC	NCC	NCC	NCC	Compatible
Glucosamine HCl: Ethyl cellulose	NCC	NCC	Slight Yellowish-brown color formation	Yellowish-brown color formation	Incompatible
Glucosamine HCl:Crospovidone	NCC	NCC	NCC	yellow color developed	Incompatible
Glucosamine HCl: PEG 6000	NCC.	NCC	NCC	NCC	Compatible
Glucosamine HCl: HPMC K200M	NCC	NCC	NCC	NCC	Compatible
Glucosamine HCl: DCP anhydrous	NCC	NCC	NCC	NCC	Compatible
Glucosamine HCl : Microcrystalline cellulose	NCC	NCC	NCC	NCC	Compatible.

NOTE: "NCC" – No color change, CC - Color change

- ✓ The infrared spectra of pure drug Glucosamine Hydrochloride and mixture of polymer and excipients were studied by FTIR spectroscopy.
- ✓ The datas are mentioned in experimental design. The results indicate that there was no physical, chemical incompatibility between drug-polymer and other excipients.

7.4. **Evaluation of granules**:-

The prepared granules of the formulations were evaluated for the parameters like bulk density, tap density, compressibility index, hausner's ratio, angle of repose, and loss on drying.

- After granulation, angle of repose was improved.
- Hausner's ratio was found to be 1.5 or less than 1.5
- Carr's index was found to be in the range of 11-12
- All the values indicated that the granules have good flow property and hence the granulation process has improved the flow property.

The tablets were formulated by wet granulation technology using the hydroxy propyl methyl cellulose K100M and K200M polymers to show the drug release with in the specification. The blended powders of different formulation were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's Ratio and drug content uniformity.

The result of angle of repose for formulations F5-F10 which indicated the good flow properties of the granules. Among them F3, F4, F9, &F10 are found to be passable.

Compressibility Index indirectly measures the flowability of powder mass for all the batches which were measured and found to be satisfactory for only F3, F4, F9 andF10 formulations respectively.

This result is an indication that the transport through the hopper into the feed frame and for subsequent die filling could be better for the formulations F3,F4, F9,F10 than F1, F2, F5, F7,&F8 because it is known that the compressibility index value below 21% indicates fair flowability of the blend.

Depending upon the ingredients of different formulations, the weight of tablet was fixed. In each formulation, weight variation was within the I.P limit. Mostly, the weight variation should not be more than ± 5%. The hardness of the all 10 formulations ranged from 21-28 kg / cm^2. All the formulations exhibited less than 1% friability.

7.5.*Invitro* release pattern of sustained matrix tablets:

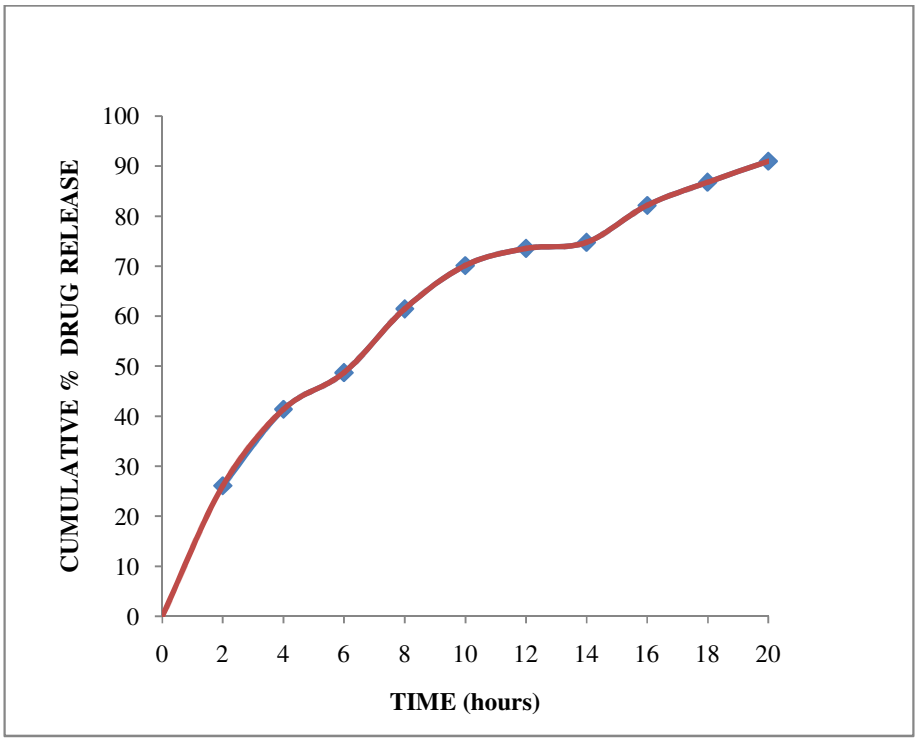
The sustained release tablet was formulated to release the drug up to 20hrs by varying the polymers and its concentration.

Invitro release study performed in distilled water, paddle type, 50rpm, reveals that the release of drug was retarded with the proportional increase of the polymer concentration. When the hydrophilic matrix tablet comes in contact with the dissolution medium, they take up water and swell, forming a gel layer around the matrix.

Then the dissolved drug diffuses out of the swollen hydrophilic matrix at a rate determined by the amount and viscosity of Hypromellose K200M in the tablet formulation. The hydrophilic polymer swells quickly & completely providing a stronger gel to prevent the immediate tablet disintegration and controlling the diffusion of the drug.

Table no: 17DISSOLUTION PROFILE OF F1 BATCH

S.No	Time (hours)	Amount of drug release(mg)	%Drugrelease	Cumulative % drug release
1	2	390	26.1	26.14
2	4	620	41.3	41.35
3	6	730	48.6	48.69
4	8	920	61.3	61.43
5	10	1050	70	70.13
6	12	1102	73.4	73.55
7	14	1120	74.6	74.76
8	16	1230	82	82.16
9	18	1300	86.6	86.78
10	20	1362	90.8	90.99



Figno: 7Dissolution profile of F1 batch

7. CONCLUSION

Glucosamine is an amino monosaccharide which is used for the treatment of osteoarthritis. Glucosamine is an essential component of mucopolysaccharides and chitin. Mucopolysaccharides (glycosaminoglycons) are large complexes of negatively charged carbohydrate chains that are incorporated into mucous secretions, connective tissue, skin, tendons, ligaments and cartilage.

Sustained release matrix tablet of Glucosamine Hydrochloride could be successfully formulated by wet granulation method with active ingredient in both intra and extra-granular part by using different viscosity grades of Hydroxy Propyl Methyl Cellulose, Avicel PH102 used as a diluent, povidone K90F used as binder, stearic acid as a lubricant. The optimized tablet formulation had showed 99.84% of drug release in 20 h. Therefore the optimized formulation containing HPMC K200M with Avicel PH102 sustained the drug release for a period of 20 h and remains throughout the studies. Among the different grades of HPMC, HPMC 200,000 cps or HPMC K200M showed the maximum retardation in drug release.

The *invitro* dissolution profile of drug release from the tablets followed zero order kinetics. From the higuchi plot of dissolution profile, we found that the drug was released by diffusion mechanism and from peppa's plot we concluded that the release mechanism was found to be non Fickian release. The optimized formulation undergoes stability study at 25°C / 60%RH, 30°C / 65%RH, 40°C /75%RH. There was no change in physical characteristics and dissolution study.

Finally, it was concluded that Sustained release matrix tablet of Glucosamine Hydrochloride can be prepared by using higher viscosity grades of HPMC as HPMC K200M had sustained the release of the drug for a prolonged time.

It is a promising approach as it can lead to release the required quantity of drug to the body, which results in minimizing the major side effect as tachycardia by minimizing the drug concentration in blood and also the entire dose is released at the target site and ultimately lead to better patient therapy.

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